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Review of

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Welcome

Hello, and a very warm welcome to this year's edition of *EMJ Rheumatology*, your source for the latest discoveries and clinical data from the field. Inside you will find a wealth of scientific papers featuring cutting-edge innovations and novel treatment avenues, as well as high-quality reviews hand-picked and compiled with the help of our esteemed editorial board. This edition also features an in-depth coverage of the European League Against Rheumatism Annual Congress (EULAR 2015), which took place this year in the beautiful city of Rome, Italy. The EMJ team were there to witness the most important developments first-hand, and as such, our exhaustive guide should prove to be a capable companion piece. The eJournal is designed to be a useful tool not just for those fortunate enough to be in attendance, but also for those unable to attend.

Included in our congress review is a round-up of reported highlights, such as a presentation of the negative effect of rheumatoid arthritis (RA) on the effectiveness of the hepatitis B vaccine, and details of a new app for smartphones and tablets that is aiding young sufferers of juvenile idiopathic arthritis in expressing and categorising their pain. Also featured are interviews with some of the preeminent voices in rheumatology and a guide to the congress awards ceremony, where prizes were given to some of the most innovative, highly regarded minds in the field. Noteworthy inclusions among the scientific papers featured here are Litwic et al., who have submitted a case study of an RA patient with diffuse large B cell lymphoma of the foot, and an article penned by Nelly Ziadé profiling axial spondyloarthritis. Along with many other features, these papers should make this edition of *EMJ Rheumatology* a must-read for rheumatologists. Spearheading our selection of articles are two symposium reviews, presented at EULAR 2015. These discuss the role of the interleukin-17 pathway in the pathogenesis of axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA), including a discussion of the unmet needs in axSpA management and a review of the effectiveness of IL-17 inhibition in PsA.

EULAR 2015 was certainly an important event, the reverberations of which will likely be felt throughout the rheumatological and medical community. We believe that the great work we saw in Rome will continue, and that this innovation will be passed on through engagement with journals such as *EMJ Rheumatology*. We would like to take this opportunity to thank you for reading, and wish you the best of luck with your future endeavours.

Spencer Gore

Team Principal, European Medical Journal

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Foreword

Dr Ian C. Chikanza

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

Dear Colleagues,

A warm welcome to this year's stimulating second edition of *European Medical Journal Rheumatology*, which focusses on reviewing the latest scientific data on osteoarthritis (OA). The traditional view of OA as a mechanical wear-and-tear disease has been revolutionised by the discovery of the key roles of local joint inflammation and cytokines. Observations on the role of obesity and predisposition to developing OA have shown that adipose tissue secretes a number of adipokines and cytokines with both local and systemic inflammatory effects. Differential expression of microRNAs between obese and non-obese osteoarthritic patients has also been demonstrated, which suggests that targeting the adipose inflammatory pathway may have therapeutic potential in OA.

> "I remain optimistic for our patients because we continue to witness major strides in the management of rheumatic conditions, and the boundaries for disease remission continue to be extended."

The review of the diagnostic criteria (ASAS) for axial spondyloarthritis will hopefully aid the management of this debilitating condition, in which anti-TNF drugs are currently only used when patients meet the New York diagnostic criteria, and by which time the best opportunity for modulating the disease may have passed. Novel pharmacological targets have been identified and drugs such as secukinumab (anti-IL-17) have been developed. Finally, we must not forget the pregnant mother who has an inflammatory rheumatic disorder: such pregnancies are high risk; the role of the rheumatologist and obstetrician in ensuring successful pregnancies in these women is reviewed.

At the European League Against Rheumatism (EULAR) conference that took place in Rome, Italy, during June, an unprecedented number of papers describing recent scientific discoveries in rheumatology and clinical trials were presented. Therapy optimisation strategies whose main objective is induction of disease remission, prevention of progression, and development of comorbidities were also presented. I remain optimistic for our patients because we continue to witness major strides in the management of rheumatic conditions, and the boundaries for disease remission continue to be extended.

In conclusion, I am very pleased to present to you this second edition of *EMJ Rheumatology* and invite you to attend the 2016 EULAR meeting in London, UK, and the 2015 American College of Rheumatology meeting in San Francisco, USA.

Yours sincerely,

Ian C. Chikanza

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

EULAR ANNUAL CONGRESS 2015

FIERA DI ROMA, ROME, ITALY

10TH-13TH JUNE 2015

Welcome to the *European Medical Journal* review of the 16th EULAR Annual European Congress of Rheumatology 2015

This year's much anticipated EULAR congress took place from 10th-13th June in the majestic city of Rome, Italy, which proved to be a fitting setting for such a fascinating and enlightening event. Rome, Italy's capital, is a sprawling, cosmopolitan city with nearly 3,000 years of globally influential art, architecture, and culture on display. Ancient ruins such as the Roman Forum and the Colosseum evoke the power of the former Roman Empire. Vatican City, headquarters of the Roman Catholic Church, boasts St. Peter's Basilica and the Vatican Museums, which house masterpieces such as Michelangelo's Sistine Chapel.

Approximately 14,000 researchers, physicians, and health professionals from nearly 120 countries descended upon Rome to attend EULAR 2015. A record number of over 4,300 abstracts were submitted, of which 82% were accepted, and over 300 were accepted as oral presentations. The programme featured 160 sessions and 35 symposia with more than 350 invited speakers. Over 40 poster tours were conducted and the poster area hosted nearly 2,000 presentations, providing a strong basis for congress proceedings.

During the opening ceremony, Prof Maurizio Cutolo, EULAR President, gave a speech outlining the continual growth and importance of EULAR as a rheumatological body, as well as the impact he expected the association to have in the very near future in terms of educating health

professionals, improving treatments, and even influencing EU health policy. "In 2017 EULAR will be a premier provider and facilitator of education at any level; physician, health professional, and patient," said Prof Cutolo.

The EULAR awards were presented at the opening ceremony. The Basic Science Abstract winners were Dr Mojca Frank-Bertoncelj (Switzerland), Dr Mohit Kapoor (Canada), Dr Simon Mastbergen (Netherlands), Dr Darren D. O'Rielly (Canada), Dr Philip Robinson (Australia), and Dr Joan Wither (Canada). The Clinical Research Abstract winners were Dr Pilar Brito-Zerón (Spain), Dr Kateri Lévesque (Canada), Mr Na Lu (USA), Dr Joost F. Swart (Netherlands), Dr Elke Theander (Sweden), and Dr William Tillett (UK).

The 2015 Edgar Stene Prize was presented to Ms Charlotte Secher Jensen (Denmark) for her essay entitled "Living in the moment". The Stene Prize is awarded in recognition of the best essay written by someone with a rheumatic or musculoskeletal disease. The EULAR Meritorious Service Award was given this year to Prof Stefano Bombardieri (Italy). The prize is awarded by the EULAR Executive Committee to rheumatologists who have made a significant contribution to rheumatology through either scientific research, clinical science, or by their activities in EULAR, national, or international organisations.

A great variety of topics in this vital area of medicine were presented and discussed in full throughout the congress. Some of the important findings on display included: a study showing that low birth weight, childhood infections, and having an older sibling are all risk factors for developing ankylosing spondylitis; a worrying analysis suggesting that the hepatitis B vaccine is less effective in patients with rheumatoid arthritis; and a report on the impact of physical trauma on the risk of developing psoriatic arthritis. In addition, Prof Helen Foster described the importance of transitional care as well as keeping people up to date with the evidence for why we need to do things better, and Dr Maarten de Wit discussed a new set of practical guidelines for producing patient content that is understandable, relevant, and effectively disseminated.

All of this and much more provided rheumatologists in attendance with a greater knowledge of the new treatments and strategies for patient care, and a heightened understanding of the significant challenges that remain. With the promise of EULAR growing in stature even further in the years to come, we can look forward to future congresses that continue to provide exciting new findings in our ongoing quest for optimal patient care.

"In 2017 EULAR will be a premier provider and facilitator of education at any level; physician, health professional, and patient."

HIGHLIGHTS

Ultrasound Diagnosis of Tenosynovitis May Predict Early RA

ULTRASOUND (US) diagnosis of tenosynovitis is superior to clinical symptoms and signs in the prediction of early rheumatoid arthritis (RA), according to study results presented at EULAR 2015.

This is the first study to prove that US-defined tenosynovitis is a strong predictor of early RA. By recognising the need to initiate treatment in RA patients earlier in the course of the disease, the procedure may lead to an improvement in clinical outcomes.

"There is a wealth of evidence that the clinical signs and symptoms of RA may be preceded by a preclinical phase lasting several years, and this preclinical phase is likely to represent an important therapeutic window within which clinical outcomes can be dramatically improved," explained Dr Andrew Filer, Rheumatology Research Group, University of Birmingham, Birmingham, UK, in a EULAR 2015 press release from 10th June 2015. "We therefore set out to explore the ability of US-defined tenosynovitis to predict very early RA during the earliest undifferentiated phase of disease."

"There is a wealth of evidence that the clinical signs and symptoms of RA may be preceded by a preclinical phase lasting several years, and this preclinical phase is likely to represent an important therapeutic window within which clinical outcomes can be dramatically improved."

Data showed that US diagnosis of tenosynovitis was superior to clinical symptoms and signs, such as early morning stiffness, symmetrical arthritis, and hand joint arthritis, in predicting early RA. The optimal minimal US data capable of predicting RA was obtained from scans of the hand flexor tendons and extensor carpi ulnaris tendons.

Clinical and multiple tendon US assessments were conducted on 107 patients with clinically apparent synovitis involving at least one joint, and symptom duration of 3 months or less. Outcomes were deduced after

18 months using the 1987 American College of Rheumatology criteria.

A blinded US assessment was performed on each patient to ascertain the presence of tenosynovitis at 16 tendon regions: bilateral fingers (extensor and flexor compartments), wrists (extensor and flexor compartments), shoulders (biceps tendon), and ankles (anterior extensors, peroneals, and posterior tibialis). The OMERACT Ultrasound Task Force recommendations were used to validate any successful diagnosis of tenosynovitis, made using grey scale and Power Doppler readings.

Reduced-Dose TNFi Therapy Safe and Effective in RA

REDUCING the dose of a tumour necrosis factor inhibitor (TNFi) by one-third resulted in a good clinical response while not leading to any increased safety risk in rheumatoid arthritis (RA) patients participating in the OPTTIRA trial, whose 6-month results were reported at EULAR 2015.

The cost of TNFi therapy is high, and therefore dose reduction strategies may be one way of reducing long-term costs. The OPTTIRA trial is a 12-month, multicentre trial designed to evaluate whether reducing the dose of a TNFi (etanercept or adalimumab) leads to a loss of clinical response in RA patients who display low disease activity and who are also receiving a synthetic disease-modifying anti-rheumatic drug.

The proportion of patients who experienced an exacerbation of symptoms and signs (flare) at 6 months was similar between the patient group that remained on the same TNFi dose (14%) and the group who reduced their dose by one-third (13%). A two-thirds reduction increased the odds of a flare occurring by four times compared with a one-third reduction, with flares taking place in 37% of patients. Adjusting the TNFi dose back to the original level was able to resolve all flares that occurred following dose reduction, with no adverse effect on progression of disabilities. There was no significant difference in self-reported measures of disability between the patient groups after 6 months, as assessed by Health Assessment Questionnaire.

"The optimal management of RA involves achieving the lowest possible disease activity – ideally remission, and then maintaining this level of control."

Around 14,000 scientists, physicians, allied health professionals and related audiences in attendance

"Our data provide an argument for updating existing disease activity cut-off points to allow RA patients with moderate disease activity to receive a biological agent in addition to conventional DMARDs."

"The optimal management of RA involves achieving the lowest possible disease activity – ideally remission, and then maintaining this level of control," explained the study's lead author, Dr James Galloway, Department of Rheumatology, King's College Hospital NHS Foundation Trust, London, UK, in a EULAR 2015 press release from 13th June 2015. "Findings from our study have shown that adopting a TNFi dose-reduction strategy can still meet this objective, with no compromise on symptom control for the patient, and offers a more cost-effective option by substantially reducing the high drug costs associated with TNFi maintenance therapy."

Risk of Joint Surgery Equal for RA Patients with Moderate and High Disease Activity

PATIENTS with rheumatoid arthritis (RA) taking conventional disease-modifying antirheumatic drug (DMARD) therapy who have moderate disease activity are at a similar risk of joint failure as those with high disease activity, according to data from a study presented at EULAR 2015.

In some countries, additional treatment with a biological DMARD is based on a disease activity cut-off that excludes RA patients with moderate disease activity. These results indicate that it is not only the RA patients with high disease activity, but also moderate RA patients, who require more intensive treatment to reduce the risk of requiring joint surgery. This reinforces the argument for implementing lower disease activity cut-off points for access to intensive treatments.

"It is well-established that sustained high disease activity in RA results in worse outcomes," said lead author Dr Elena Nikiphorou, Rheumatology Department, St Albans City Hospital, St Albans, UK, in a EULAR 2015 press release from 10th June 2015. "In reality, however, many treated RA patients remain in low or moderate disease activity states and their outcomes, especially in the long term, are less well studied."

The study enrolled a total of 2,071 RA patients, 2,044 of whom had at least two drug activity states (DAS) recorded between Years 1–5: 21% were in remission, 15% in low DAS, 26% in low-moderate DAS, 21% in high-moderate DAS, and 18% in high DAS categories.

After controlling for numerous factors, including age at disease onset and gender, patients with low-moderate DAS, high-moderate DAS, and high DAS categories were all predictive of an increased risk of major joint surgery ($p<0.005$).

With respect to immediate surgery, however, high-moderate DAS and high DAS predicted a higher risk than patients with low-moderate DAS or low DAS ($p=0.034$ and $p=0.001$, respectively).

"Our data provide an argument for updating existing disease activity cut-off points to allow RA patients with moderate disease activity to receive a biological agent in addition to conventional DMARDs," concluded Dr Nikiphorou.

Hepatitis B Vaccine Compromised in RA Patients

INDIVIDUALS with rheumatoid arthritis (RA) are less likely to be protected by hepatitis B vaccination than the general population, according to the results of a trial presented at EULAR 2015.

Within the study only 11% of RA patients responded to the vaccine, compared with 83% of those without RA, indicating that RA patients could remain at risk of infection in spite of vaccination. This marks another disadvantage for sufferers of RA, who are at greater risk of contracting life threatening infections compared with non-sufferers.

"The majority of RA patients tested as part of our study were not protected by hepatitis B vaccination," said study investigator Dr Misha Tilanus, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, in a EULAR 2015 press release from 12th June 2015. "People with RA have an increased risk of morbidity and mortality from infections, and to discover that immunisation might not confer protection is a real concern. It is crucial that patients and healthcare practitioners are aware of this lack of efficacy and do all they can to minimise risk."

"People with RA have an increased risk of morbidity and mortality from infections, and to discover that immunisation might not confer protection is a real concern."

The international prevalence of RA varies between 0.3-1.0% and is more common among women and in developed countries. Along with many of its treatments, RA may suppress the immune system, leaving patients at risk of a potentially fatal infection.

Over the course of the study, vaccination with HBVAXPRO-10 was performed according to the standard regimen (0, 1, and 6 months), with markers of response to the vaccine (hepatitis B antigens, anti-HBsAG) determined after 28 weeks. It was found that RA patients had a higher risk for non-response than controls, with an odds ratio of 44 (corrected for age and gender). There was no difference in response between

patients using anti-tumour necrosis factor treatment, disease-modifying anti-rheumatic drugs, or rituximab.

Biologic Therapies Potentially Pose No Risk at Conception for Patients with Rheumatic Diseases

EXPOSURE to biologic therapies around the time of conception does not increase the risk of malformations or other harmful neonatal consequences in patients with rheumatoid arthritis (RA) or spondyloarthropathies, according to promising new data from RABBIT, the German biologics registry, which was presented at EULAR 2015.

Conventional disease-modifying antirheumatic drugs (DMARDs) such as sulfasalazine, cyclosporine, and azathioprine, remain valid treatment options for pregnant patients because their safety profile is known. However, new biologic DMARD therapies are relatively unproven in pregnancy. Tumour necrosis factor inhibitors, the most widely researched of the biologic DMARDs, can be implemented before conception and during the first and early second trimester. Their use in late pregnancy poses a far greater risk of negative outcomes, however, and, like many other biologic treatments, their use must be based on the severity of maternal disease.

With this in mind, data such as those included in the RABBIT registry are vital for development of more optimal treatment options and building a broader, more exhaustive archive of knowledge on biologics. The research, which was presented by Dr Anja Strangfeld, German Rheumatism Research Center, Berlin, Germany, in a recently-written report published in EULAR Daily Congress News, Issue 1, on the 10th June 2015, analysed 95 pregnancies in 78 women between 2001 and 2011. In the 35 pregnancies in which biologic DMARDs were stopped at least 4 weeks before conception, 4 spontaneous abortions were recorded (11%), while there were 10 spontaneous abortions identified among the 51 pregnancies exposed to biologic DMARDs at conception (20%).

Nine patients were naïve to biologic therapy. These rates are reassuringly similar across treatment regimens and also lie within the range observed in the general public (15-20%), indicating that their use could be a viable option for prospective mothers.

Hydroxychloroquine Ineffective in Killing Pain of Hand Osteoarthritis

APPLICATION of the disease-modifying anti-rheumatic drug hydroxychloroquine (HCQ) over a 24-week period does not reduce mild-to-moderate pain in primary hand osteoarthritis (OA) patients, according to data from an interventional trial presented at EULAR 2015.

"The findings from our trial do not support the prescription of HCQ for patients with mild-[to-] moderate pain from hand OA, neither on a physical nor emotional level."

Currently the treatment of OA is limited, as the pharmacological treatment options available are only proven to work for short periods of time and are not effective for all patients, causing side-effects that can restrict use. This poses a problem as OA is the most common form of arthritis. The condition, which causes severe joint pain and disability, affects around 8% of people aged 60 or over, and 26% and 13% of women and men aged 70 or over.

Between July 2010 and December 2013, 202 patients aged 40 years and over with primary hand OA were enrolled from rheumatology clinics at six hospitals in the Rotterdam area. The patients were randomly assigned to receive either oral HCQ 400 mg once a day (n=100) or placebo (n=102) for 24 weeks.

The primary outcome for the study was a decrease in hand pain in the previous 24 hours, following 24 weeks of therapy, as evaluated on a visual analogue scale. The results revealed that HCQ did not significantly reduce pain in symptomatic hand OA when compared with placebo. Furthermore, HCQ had no overall effect on pain, disability, and joint stiffness, and no overall change was seen in physical, social, and emotional wellbeing scores, as measured by Arthritis Impact Measurement Scale 2 SF scales.

"The findings from our trial do not support the prescription of HCQ for patients with mild-[to-]moderate pain from hand OA, neither on a physical nor emotional level," said lead researcher Mrs Natalja M. Basoski, Department of Rheumatology, Maasstad Ziekenhuis, Rotterdam, Netherlands, in a EULAR 2015 press release from 13th June 2015. "However, further investigations will need to be performed to determine whether HCQ relieves pain in other specific phenotypes of hand OA."

Physical Trauma Linked to PsA Onset in Psoriasis Patients

ELEVATED risk of developing psoriatic arthritis (PsA) has been observed among psoriasis patients exposed to physical trauma, especially when the trauma involved bone and/or joints, according to the results of a large population study presented at EULAR 2015.

PsA occurs in 1-3% of the population and up to 30% of those who suffer from psoriasis. Previous studies suggested the idea of a 'deep Koebner' affecting PsA, previously a phenomenon seen in skin psoriasis; it was found that when a patient with psoriasis had an area of skin that became traumatised following an injury, a psoriatic lesion frequently appeared in the same region. A deep Koebner's phenomenon involves deeper tissues including bones and joints and could play a role in PsA.

Using data gathered between 1995 and 2013, 15,416 psoriasis patients exposed to trauma and 55,230 unexposed controls were identified and followed up for a total of 425,120 person-years, during which 1,010 incident PsA cases were noted. The incidence rate of PsA among psoriasis patients not exposed to trauma was 22 per 10,000 person-years compared with 30 per 10,000 in the exposed group.

Following adjustments for age, gender, date of entry into the patient database, duration of psoriasis, body mass index, smoking, alcohol consumption, and number of visits to the general practitioner, patients exposed to trauma were shown to have an increased risk of PsA compared with controls.

A subset analysis revealed that while bone and joint traumas were associated with increased PsA risk, nerve and skin traumas were not. Furthermore, patients without psoriasis exposed to trauma did not carry an increased risk of developing rheumatoid arthritis.

"Our findings highlight the importance [of] further study into the complex factors that lead to arthritis in psoriasis patients, as we may find ways to modify the risk once we fully understand it," said the senior author of the study, Dr Thorvardur Love, Assistant Professor of Rheumatology, Landspitali University Hospital, Reykjavik, Iceland, in a EULAR 2015 press release from 11th June 2015.

An App-t Way for Young JIA Patients to Express Their Pain

INTERACTIVE iPad app has been found to help young individuals with juvenile idiopathic arthritis (JIA) to describe their pain, according to study data presented at EULAR 2015.

"Our findings highlight the importance [of] further study into the complex factors that lead to arthritis in psoriasis patients, as we may find ways to modify the risk once we fully understand it."

"'This Feeling!' uses familiar technology that children and young people are comfortable with, encouraging them to describe the pain type, intensity, location, spread, and emotional impact at a given time, by using an interactive manikin, adjustable pain icons, facial expressions, drawing tools, and free text description."

Nearly all of the children studied preferred the new digital tool, aptly named 'This Feeling!', to other conventional methods and felt that it was an interesting and engaging way to express their experiences of pain.

"It is vital for children and young people to be able to communicate about their pain in order for them to access the best possible support to manage their condition long term," said Prof Wendy Thomson, Inflammatory Arthritis in Children Lead at the NIHR Manchester Musculoskeletal Biomedical Research Unit, Manchester, UK, in a EULAR 2015 press release from 11th June 2015. "'This Feeling!' uses familiar technology that children and young people are comfortable with, encouraging them to describe the pain type, intensity, location, spread, and emotional impact at a given time, by using an interactive manikin, adjustable pain icons, facial expressions, drawing tools, and free text description. The app is a simple multidimensional approach to pain management that allows those with JIA to communicate the intricacies of their pain."

The subjective nature of pain poses a challenge to understand the extent to which patients are feeling pain, particularly in children. "Despite advances in the diagnosis and treatment of JIA, pain is still poorly managed and this is distressing for both children and their parents. For every individual the feeling is unique, which can be hard to explain effectively, and for children, communication barriers also play a key role," added Prof Thomson.

Individuals aged between 5 and 16 years were enrolled in a study comparing conventional self-report measures (visual analogue scale and the Faces Pain Scale – Revised) with 'This Feeling!'. Data showed that 95% of children preferred using the app over the other conventional methods, finding it easier and much more interesting to use. Parents commended the app for capturing the complexity of pain in a child-friendly manner, which other conventional methods failed to do.

Environmental Factors Increase Risk of Ankylosing Spondylitis

DIAGNOSIS of ankylosing spondylitis (AS) may be predicted by low birth weight, having older siblings, and hospitalisation for infection between the ages of 5-16 years, according to the results of a study presented at EULAR 2015.

These data indicate that environmental factors, alongside established genetic associations, play a crucial role in the pathogenesis of AS and represent a breakthrough in determining the origin of the disease. The cause of AS is currently unknown but is strongly linked with the genotype HLA-B27, although not everyone testing positive for the marker will go on to develop the disease.

"A link between AS and the HLA-B27 genotype was established more than 3 decades ago, yet studies on the environmental risk factors are few," said study investigator Dr Ulf Lindström, Institute of Medicine, Rheumatology and Inflammation Research, Sahlgrenska Academy, Gothenburg, Sweden, in a EULAR 2015 press release from 11th June 2015. "Our research has identified three factors associated with significantly increased risk of the disease in later life. These data strengthen our understanding of the interplay between genetics and environment in AS, and bring us closer to pinpointing the underlying cause of the disease."

Statistically significant increased risk was seen for birth weight <3,000 g (18% versus 15%), having older siblings (63% versus 58%), and for hospitalisation due to infection between the ages of 5-12 years (5% versus 3%) and between 13-16 years (2% versus 1%). These risk factors have also emerged in other associated conditions: the catalysing effect of infections in reactive arthritis, the predictive potential of birth weight for the development of autoimmune disease (diabetes and rheumatoid arthritis), and a connection between older siblings and disease risk in asthma have all been established.

"These data strengthen our understanding of the interplay between genetics and environment in AS, and bring us closer to pinpointing the underlying cause of the disease."

The study utilised data from numerous Swedish national registers, with five matched controls (sex, age, county) included for every case of AS. Factors assessed included: birth weight, gestational age, type of birth (single/multiple), number of older siblings, and exposure to infections.

Epigenetic Factors Implicated in Progression of Ankylosing Spondylitis

DNA methylation could influence the progression of structural damage to the joints and spine in ankylosing spondylitis (AS), according to data presented at EULAR 2015.

These results demonstrate significant associations between a low methylation score and further radiographic progression of the disease, while smoking has been implicated in worsening the disease outcome.

"We hypothesise that environmental triggers – such as smoking – could lead to epigenetic changes that accelerate the damage caused by the disease, and that investigating the mechanisms that control these changes could one day lead to novel therapeutic targets for AS."

Epigenetic mechanisms such as DNA methylation are crucial for controlling regular development, however abnormal epigenetic change may be observed when they are implicated in disease. This change may be catalysed by environmental hazards including smoking, and the study team believe that investigation of the underlying mechanisms may eventually lead to new targets for AS treatment.

"This is the first study to demonstrate how epigenetic factors can influence radiographic progression in AS," said study investigator Dr Proton Rahman, Faculty of Medicine, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador, Canada, in a EULAR 2015 press release from 12th June 2015. "We investigated epigenetic variants recently linked to ankylosis, and uncovered a significant association between smoking, methylation status, and radiographic progression. We hypothesise that environmental triggers – such as smoking – could lead to epigenetic changes that accelerate the damage caused by the disease, and that investigating the mechanisms that control these changes could one day lead to novel therapeutic targets for AS."

The study consisted of 76 AS patients who received radiographs every 3 years on average, with 35 of these patients displaying radiographic progression. The results showed a significant association between smoking, methylation status, and radiographic progression; a low methylation score was significantly associated with further radiographic progression, and worse radiographic progression was seen in smokers versus non-smokers (not statistically significant).

Damage caused by AS disables spinal mobility, diminishing a patient's ability to perform daily activities and negatively affecting their quality of life. Radiography is the traditional tool for recognising these structural changes.

New Genetic Variants Linked with Autoinflammatory Diseases

NOVEL genetic variants that could be linked with susceptibility to paediatric autoinflammatory diseases have been discovered by means of an emerging diagnostic tool called the next generation sequencing (NGS), according to data presented at EULAR 2015.

The NGS process enables the identification of many genetic variants that could be associated with disease susceptibility, but the major challenge lies in interpreting their clinical relevance.

The research, presented by co-author Dr Elisa Pisaneschi, Cytogenetics and Molecular Genetics Unit, 'Bambino Gesù' Children's Hospital, IRCCS, Rome, Italy, in a recently-written report published in EULAR Daily Congress News, Issue 1, on the 10th June 2015, detailed how the authors genetically diagnosed autoinflammatory disorders using NGS and found that mutations in >15 genes affecting several distinct pathways are associated with recessive and dominant autoinflammatory syndromes.

A total of 145 patients who attended the centre from 2010-2014 were enrolled with undefined autoinflammatory disorders. To expediate the diagnosis, the researchers began by investigating 11 genes previously shown to be involved in autoinflammatory disorders, and these were divided into two panels: Panel 1 consisted of the genes *MVK*, *MEFV*, *NRLP12*, *NRLP3*, *NOD2*, *TNFRSF1A*, and *PSTPIP1*; and Panel 2 consisted of *IL1RN*, *LPIN2*, *IL36RN*, and *PSMB8*.

There were 61 patients found to be carrying variants in the genes of Panel 1, with a detection rate of 42%. Some of the variants identified by the study were novel while others were previously established polymorphisms, some being known risk factors and several with unknown pathogenic significance. In just under one-third of patients, a combination of variants in two different genes was found. Because these patients show variants in multiple analysed genes, it can be hypothesised that different variants in different genes may cooperate to determine a pathological phenotype.

The NGS process enables the identification of many genetic variants that could be associated with disease susceptibility, but the major challenge lies in interpreting their clinical relevance. In particular, variants that are found at a relatively low frequency are particularly challenging because they may function as susceptibility alleles for inflammation rather than disease-associated mutations.

Unique Microbial Fingerprint Could Lead to Enhanced Diagnosis and Treatment of SSc

PATIENTS with systemic sclerosis (SSc) have a unique bacterial signature in their colon compared with healthy individuals, according to study data presented at EULAR 2015.

These results suggest that changes in the gut ecology may contribute to the clinical symptoms of SSc and could be used to improve diagnosis of the disease, thus paving the way for the development of alternative targeted treatments. This study is the first

to directly investigate the microbial composition of the colon, and indicates that an imbalance in bacteria is a key characteristic of SSc.

A total of 17 patients with SSc received colonoscopy and were scored for distention/bloating, faecal soilage, diarrhoea, constipation, emotional wellbeing, and social functioning. The composition of microbial communities from the first section of the large intestine (caecum) and the last section of the large intestine (sigmoid) were compared with those from healthy individuals.

"By identifying significant differences in bacteria – both in type and quantity – seen in the colons of healthy individuals and those with SSc, we hope to have pinpointed the exact changes in body ecology that may contribute to the clinical symptoms of this disease."

The results highlighted significant differences between patients with SSc and healthy individuals. There was a noticeable decrease in specific bacteria known to supply essential nutrients (commensal bacteria; *Bacteroides* and *Faecalibacterium*), and an increase in infection-causing bacteria (pathogenic bacteria; *Enterobacteriales* and *Fusobacterium*).

"Although gastrointestinal tract dysfunction is a major cause of morbidity and mortality in patients, its aetiology has always remained elusive," said study investigator Dr Elizabeth Volkmann, David Geffen School of Medicine, University of California, Los Angeles (UCLA), Los Angeles, California, USA, in a EULAR 2015 press release from 11th June 2015.

"By identifying significant differences in bacteria – both in type and quantity – seen in the colons of healthy individuals and those with SSc, we hope to have pinpointed the exact changes in body ecology that may contribute to the clinical symptoms of this disease. We believe investigating this specific microbial signature further has the potential to lead to better diagnostic tools and treatment for a truly debilitating condition."

Biologics May Lessen Economic Burden in Rheumatic Disease

BIOLOGICS improve both absenteeism (not attending work) and presenteeism (attending work but not functioning fully) in patients with chronic inflammatory arthritides, according to data from a systematic review of published studies presented at EULAR 2015.

Chronic inflammatory arthritides – including rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) – confer substantial patient and economic burdens. As a result of their condition, one-fifth of patients with rheumatic conditions have been forced to change career, one-third will have stopped working within 2 years of onset, and half will be unable to work within 10 years.

"Within a few years of diagnosis, a significant proportion of those suffering from RA, AS, and PsA are no longer able to work. This has major financial consequences for individuals and society, and is one of the reasons the indirect costs are higher for rheumatic disease than

other diseases," said study investigator Dr Cécile Gaujoux-Viala, Head of the Department of Rheumatology, Nîmes University Hospital, Nîmes, France, in a EULAR 2015 press release from 12th June 2015. "Our systematic review demonstrates the beneficial effects of biologics on absenteeism and presenteeism, leading us to suggest that the high costs of these treatments could in fact be at least partly offset by the savings they deliver in indirect costs."

15,881 patients with RA, AS, and PsA received biological agents in 15 randomised controlled trials and 7 controlled cohorts, and the effects were compared to 9,713 patients who received non-biologics. The outcomes measured were accumulated missed workdays, the number of patients losing work time, impact on productivity, and employment loss. The studies showed that biologics significantly reduced the number of missed workdays, improved work productivity, and can potentially reduce the economic burden of rheumatic conditions on patients and society as a whole.

Anti-TNFs Help PsA Patients Return to Work

ANTI-TUMOUR necrosis factor (anti-TNF) agents are slightly more effective than conventional disease-modifying antirheumatic drugs (DMARDs) when assisting psoriatic arthritis (PsA) patients with work issues, according to study results presented at EULAR 2015.

350 invited speakers

"Improvement in work disability and disease activity was greater and more rapid amongst those commenced on anti-TNF. This study suggests that work disability is reversible in the real-world setting."

"We observed a clinically significant improvement in presenteeism, productivity loss, and disease activity after initiation of DMARD and anti-TNF treatment. Improvement in work disability and disease activity was greater and more rapid amongst those commenced on anti-TNF. This study suggests that work disability is reversible in the real-world setting," said the investigators, led by Dr William Tillett, Department of Rheumatology, Royal National Hospital for Rheumatic Diseases, Bath, UK, in a recently written report published in EULAR Congress News, Wednesday Edition, on the 10th June 2015.

The study derives from the Long-term Outcomes in Psoriatic ArthritiS (LOPAS II) working group, a 2-year, multicentre, observational cohort study of work disability in PsA. The study aimed to discover how treatment affects work performance in PsA patients. At baseline, prior to treatment with anti-TNFs or DMARDs, the LOPAS II team found that 164 (41%) of the 400 enrolled patients were unemployed. Treatment of this group with either anti-TNFs or DMARDS had no effect on overall employment levels.

However, of the 236 subjects working at baseline, presenteeism improved from 40-10% and productivity loss improved from 45-10% among patients who began taking anti-TNFs.

The benefits of DMARD treatment were modest in comparison; presenteeism improved from 30-20% and productivity loss from 40-25%. The difference in change of presenteeism between the two treatment groups became statistically significant at 2 weeks and remained so at 24 weeks.

EULAR is the umbrella organisation which represents the patient, health professional and scientific societies for rheumatology across the EU

Over 24 weeks, median scores on the Disease Activity Index for Psoriatic Arthritis improved from 53 to 14 among anti-TNF patients, which is considered a good response, but only improved from 39 to 30 in DMARD patients, considered a poor response. The data revealed a "surprisingly poor clinical response to synthetic DMARDs on clinical outcomes [...] opposed to good response amongst patients commenced on TNF inhibitors," said Dr Tillett.

Pre-Screening Identifies Paediatric Rheumatic Disease Patients Eligible for Varicella Vaccination

VARICELLA vaccine may be safe and efficacious even in children with paediatric rheumatic disease receiving immunosuppression treatment, according to data presented at EULAR 2015.

By using a checklist to pre-screen children, the researchers were able to recognise diverse patient groups suitable for vaccination, thus protecting them from a life-threatening illness. This process would allow immunocompromised children receiving the vaccine to continue their treatment course without the threat of disease onset.

Rheumatic diseases, a subset of autoimmune diseases, are usually treated with immunosuppressant drugs to compromise the immune response; however, this immunosuppression also exposes patients to further risk of infection.

Yet the study proved that even children who are receiving immunosuppression treatment can receive the vaccine and remain safe from infection. Twenty-one varicella zoster virus (VZV)-

susceptible children aged 2-18 who were receiving immunosuppression therapy for clinically inactive paediatric rheumatic diseases, including juvenile idiopathic arthritis and connective tissue diseases, were screened using the immunologic checklist prior to vaccination. Patients meeting the safety criteria received either a first or second dose of the vaccine without interruption of their immunosuppression therapy.

An examination after 4 weeks revealed no indication of vaccination-induced varicella in any of the children, and none required treatment change or suffered a disease flare.

"By pre-screening children using easy-to-obtain immunological criteria, we were able to safely and effectively vaccinate a major group of immunocompromised children, without having to stop their treatment."

"Although chickenpox is a common and often mild childhood illness, it can be life-threatening in children with a suppressed immune system, such as those being treated for rheumatic disease. While a vaccine is available, its safety in children receiving immunosuppression has long been debated," explained study investigator Dr Fabian Speth, German Center for Pediatric and Adolescent Rheumatology, Garmisch-Partenkirchen, Germany, in a EULAR 2015 press release from 12th June 2015.

"By pre-screening children using easy-to-obtain immunological criteria, we were able to safely and effectively vaccinate a major group of immunocompromised children, without having to stop their treatment. This is a significant development in preventing a persisting, and sometimes fatal, virus."

Triple DMARD Therapy Improves Functional Ability in Early RA

INTENSIVE treatment of early rheumatoid arthritis (RA) with a triple disease-modifying anti-rheumatic drug (DMARD) regimen could provide significant patient benefits when compared with monotherapy, according to results from the tREACH trial presented at EULAR 2015 by the lead author of the study, Dr Angelique Weel, Department of Rheumatology, Maasstad Hospital, Rotterdam, Netherlands, in a EULAR 2015 press release from 10th June 2015. Intensive combination therapy initiated early in the disease course is in contrast to the more common, escalating, stepwise approach to pharmacotherapy in RA patients.

The tREACH trial randomised a total of 281 RA patients to receive either a triple DMARD regimen of methotrexate, sulfasalazine, and hydroxychloroquine with bridging glucocorticoid, or monotherapy with methotrexate alone (with glucocorticoid). Improvement in the functional ability of patients, as assessed by Health Assessment Questionnaire scores, was significantly greater in the triple DMARD group after only 3 months of treatment and throughout the first 2 years of therapy, irrespective of disease activity. Assessment of joint damage with X-rays showed that progression was minimal and similar between the two treatment groups. The proportion of

patients in each group who achieved sustained remission (DAS44 score <1.6 at two consecutive time points) was also similar, as was the prevalence of flares occurring after the tapering of therapy in both groups.

Dr Weel summarised the results of the study: "Our data showed an earlier decrease in disease severity and improvements in functional ability in the combination-therapy groups compared to monotherapy, adding to the evidence base for an intensive treatment approach early on. And with significant numbers of patients achieving drug-free remission using less expensive biologicals during the first 2 years of therapy, these data should alleviate concerns regarding the need for long-term aggressive therapy."

"Our data showed an earlier decrease in disease severity and improvements in functional ability in the combination-therapy groups compared to monotherapy, adding to the evidence base for an intensive treatment approach early on."

BEST ABSTRACT AWARD WINNERS AT EULAR 2015

The winners of the 12 Abstract Awards presented at this year's EULAR congress addressed a wide range of topics in the field of rheumatology, with six awards presented for abstracts focussing on basic science and six awarded for clinical research. The global reach of the congress was reflected in the diverse origins of the award winners, with researchers from Canada claiming 4 of the 12 prizes, another 2 being awarded to authors from Utrecht in the Netherlands, and a single award going to each of Australia, Spain, Sweden, Switzerland, the UK, and the USA.

New treatments and improved management of complications and comorbidities have improved the survival of RA patients over the past decade.

Fundamental and clinical aspects of rheumatoid arthritis (RA) and its sequelae continue to be a key focus of the work presented at the EULAR congresses, as well as a considerable part of the caseload of rheumatologists worldwide. Utilising general population data from the UK's Health Improvement Network database, Na Lu was able to demonstrate that new treatments and improved management of complications and comorbidities have improved the survival of RA patients over the past decade. The RA cohort and a matched non-RA control cohort were each divided into two subgroups based on the year of diagnosis (either 1999-2005 or 2006-2012). Patients with RA and in the earlier diagnosis subgroup displayed a considerably higher mortality rate compared with those RA patients in the more recent diagnosis subgroup (23.8 vs 15.7 cases per 1,000 person-years), while a more modest improvement was seen in the corresponding two subgroups of the control cohort (14.1 vs 11.1 cases per 1,000 person-years). The hazard ratios (HRs) for mortality in the two RA patient subgroups were 1.51 (95% confidence interval [CI]: 1.33-1.72) for those with earlier diagnosis and 1.21 (95% CI: 1.05-1.39) (p for interaction=0.027) for those with more recent diagnosis, which suggests that modern therapeutic strategies may be providing substantial benefits.

The molecular mechanisms driving the development of RA were the focus of the study described in Mojca Frank-Bertoncelj's abstract, which investigated variations in the transcriptomes of synovial fibroblasts (SFs, which drive local joint destruction in RA) isolated from different joint locations. The study compared RNA expression patterns in SFs isolated from the metacarpophalangeal (MCP), shoulder, and knee joints of RA and osteoarthritis (OA) patients, and from healthy human knees, as well as comparing SFs isolated from the front paws, ankles, and knees of wild-type and tumour necrosis factor alpha (TNFα) transgenic arthritic C57BL/6 mice. Analysis of the RNA expression

patterns demonstrated clustering of human SFs according to anatomic joint location rather than primary disease, with small noncoding RNA conferring the strongest positional identity. Furthermore, RNA patterns relating to several arthritis-relevant pathways (e.g. chemotaxis, cell adhesion, JAK/STAT inflammatory pathway) were enriched in a joint-specific manner. These locational differences in SF transcriptomes suggest that functionally unique subsets of these cells populate different joints, and the existence of epigenetically imprinted, positional 'risk' signatures may increase the susceptibility of certain joints to destructive arthritis.

Functionally unique subsets of these cells populate different joints, and the existence of epigenetically imprinted, positional 'risk' signatures may increase the susceptibility of certain joints to destructive arthritis.

Analysis of differential gene expression was also reported in Simon Mastbergen's abstract that addressed the transcriptional response initiated following joint distraction in an experimental canine model of knee OA. Joint distraction provides long-term improvement of pain and function in OA patients, and is accompanied by intrinsic cartilage repair through processes that are not well understood. Knee tissue samples taken from the fat pad, synovium, meniscus, bone, and cartilage of animals either receiving joint location or not were compared with regard to the transcription of 35 regenerative gene markers. The animals receiving joint distraction displayed downregulation of typical OA markers and maintenance of genes known to be involved in matrix remodelling during regeneration, e.g. aggrecanase. Furthermore, genes regulating several pathways, including the transforming growth factor beta (TGF-β), Wnt, and Notch signalling pathways, were differentially expressed between the treatment and untreated groups, which suggests that joint distraction initiates transcriptional regulation of several important regenerative genes that ultimately leads to cartilage repair.

Genetic analysis also featured in Philip Robinson's study that aimed to identify genetic variants associated with the risk of developing ankylosing spondylitis (AS). It has been known for some time that AS is associated with human leukocyte antigen (HLA)-B27, as well as other HLA variants and many non-MHC loci, but a significant contribution from other heritable factors remains to be characterised. Microarray analysis of 5,040 AS patients and 21,133 healthy controls revealed novel associations achieving genome-wide significance in *USP8* and *CDKAL1*, as well as suggestive associations with common variants in *FAM118A*, *C7orf72*, and *FAM114A1*. A low frequency association was found in *PNPLA1* at a suggestive level of

significance. Not only did the study identify new genetic associations for AS, but it also provided additional evidence for a similarity in aetiopathogenesis between AS and inflammatory bowel disease (IBD), as three of the novel variants identified have been previously associated with IBD, and one previously associated with low hip bone mineral density.

Ephrin-B2 may be an important mediator of fibrogenesis in SSc and represent a novel target for the design of rational therapies.

Identification of fundamental mechanisms of disease was also the subject of Mohit Kapoor's abstract describing a potential role for the transmembrane protein ephrin-B2 in the fibrinogenesis that occurs in systemic sclerosis (SSc) patients, and which is characterised by the differentiation of fibroblasts into myofibroblasts and deposition of extracellular matrix. Previous microarray studies have shown that ephrin-B2 is overexpressed in fibroblasts isolated from SSc patients, but this study went further by using a variety of techniques to demonstrate the profibrotic effects of this protein.

For example, the addition of recombinant ephrin-B2 to normal human skin fibroblasts *in vitro* induced myofibroblast formation, the subcutaneous treatment of mice with recombinant ephrin-B2/Fc induced significant skin fibrosis, and fibroblast-specific ephrin-B2 knockout mice were significantly protected from bleomycin-induced lung and skin fibrosis. The expression of ephrin-B2 was also shown to be elevated in SSc fibroblasts and skin sections from idiopathic pulmonary fibrosis patients, while soluble ephrin-B2 was found at a higher concentration in bronchoalveolar lavage samples from SSc patients and bleomycin-challenged mice, and was capable of inducing fibroblast chemotaxis. Taken together, these observations suggest that ephrin-B2 may be an important mediator of fibrogenesis in SSc and represent a novel target for the design of rational therapies.

Patients with systemic autoimmune rheumatic diseases (SARDs), such as SSc, often exhibit a pre-clinical phase in which they test positive for anti-nuclear antibody (ANA) but lack clinical symptoms. The study reported by Joan Wither investigated the change from an asymptomatic to clinical disease state in order to identify whether this progression was accompanied by immunological changes that could be used as a means of predicting disease onset. In order to generate an 'IFN5 score', the expression of five interferon (IFN)-induced genes was analysed in healthy controls and 95 SARD patients (either SSc, systemic lupus erythematosus [SLE], Sjögren's syndrome [SS], mixed connective tissue disease [MCTD], or dermatomyositis) who were either ANA-positive but asymptomatic for SARD, ANA-positive and with at least one symptom of SARD

(i.e. undifferentiated connective tissue disease [UCTD]), or ANA-positive and with a recent SARD diagnosis. Patients who were asymptomatic and those with UCTD, SS, or SLE displayed significantly higher IFN5 scores compared with healthy controls. There were also marked elevations in IFN5 scores in subsets of asymptomatic and UCTD patients, which could not be explained by recent infection. There was a significant correlation between the ANA titre and IFN5 score for all ANA+ individuals, except in aymptomatic individuals and those with UCTD. The results from this study therefore suggest that there is an IFN signature occurring in a subset of ANA-positive individuals prior to a confirmed diagnosis of SARD, but this appears to correlate with the type and number of specific ANAs rather than with the onset of clinical disease.

Patients who present at diagnosis of primary SS with an ESSDAI score ≥14 should be considered part of a high-risk population and should be followed more closely than those with no systemic activity.

Once a SARD is diagnosed, it is important to identify those patients at high risk of a poor prognosis in order to allow early initiation of therapy and/or more intensive treatment options. The abstract of Pilar Brito-Zerón described the association of baseline systemic disease activity (as measured using ESSDAI scores to define their disease activity state [DAS] as either 'low' [ESSDAI <4], 'moderate' [ESSDAI between 5 and 13], or 'high' [ESSDAI >13]) with poor outcomes (lymphoma or death) in patients with primary SS. At diagnosis, 11% of patients showed a high DAS, 32% showed a moderate DAS, and 35% a low DAS, with 22% having no systemic activity (ESSDAI of 0). Patients displaying a high DAS at diagnosis were more likely to develop haematological neoplasia and have poor survival compared with patients without systemic activity (19% vs 2%, p<0.001 and 19% vs 11%, p=0.032, respectively). The occurrence of cancer was more frequent in patients with a high DAS at diagnosis compared with those without high baseline activity (21% vs 10%, p<0.001); however, a high DAS was related to a higher frequency of haematological neoplasia but to a lower frequency of solid neoplasia (18% vs 2.5% and 2.9% vs 7.5%, respectively; both p<0.001). The implication of these results is that patients who present at diagnosis of primary SS with an ESSDAI score ≥14 should be considered part of a high-risk population and should be followed more closely than those with no systemic activity.

Relationships between demographic variables and disease activity were also the subject of Elke Theander's abstract that described the observation of a reduced risk of primary SS in individuals who smoke and an increased risk of developing the disease in those who cease to smoke. The study investigated incident cases of primary SS occurring in participants of two population-based surveys of more than 30,000 individuals each, and identified 63 individuals diagnosed with primary SS a median of 98 months (range: 3-329) after inclusion. Current smoking at inclusion was associated with a reduced risk of subsequent diagnosis of primary SS (odds ratio [OR]: 0.26, 95% CI: 0.11-0.60) and being a former smoker was associated

with an increased risk of primary SS (OR: 8.1, 95% CI: 3.2-21 compared with current smokers; OR: 4.1, 95% CI: 1.8-10 compared with never smokers). Cessation of smoking was not related to symptoms of SS as these appeared >5 years after smoking cessation in 91% of cases. The precise protective mechanism relating to smoking and its role in autoimmunity are unclear, but smoking has also been previously shown to be beneficial or protective in sarcoidosis, ulcerative colitis, and Parkinson's disease.

Prediction of prognosis was also investigated by Kateri Lévesque whose abstract reported the identification of variables associated with survival following congenital heart block (CHB) in cases of neonatal lupus syndrome (NLS). The study retrospectively analysed data from the French national NLS registry and identified hydrops and prematurity as factors associated with feto-neonatal deaths in this group. During a median follow-up of 7 years (range: birth to 36.1), 79.1% of surviving children received a pacemaker, 18.8% had dilated cardiomyopathy (DCM), and 11.8% died. The only factor associated with late mortality in children who survived the neonatal period was postnatal DCM (neonatal or late-onset DCM) (HR: 36.48, 95% CI: 8.11-164.13; p<0.0001). The probability of survival at 10 years of age for a child with CHB born alive was 87.1%, which dropped to 23.1% in the presence of neonatal DCM and dropped to 53.9% in those who developed a late-onset DCM requiring treatment, versus a survival of 98.6% in those without DCM. The factors associated with neonatal DCM were found to differ completely from those associated with late-onset DCM. In multivariate analyses, only *in utero* DCM was associated with neonatal DCM (HR: 15.99, 95% CI: 3.93-65.01; p=0.0001), whereas only non-white ethnicity was associated with late-onset DCM (HR: 3.65, 95% CI: 1.28-10.0; p=0.0147). In addition to identifying these prognostic factors, the study findings failed to support the use of fluorinated steroids for CHB due to the lack of any association between fluorinated steroid treatment *in utero* and CHB regression, survival, or the absence of late-onset DCM.

Differential responses between patients either responsive or non-responsive to treatment can shed new light on fundamental mechanisms of disease and suggest new therapeutic targets. Darren D. Rielly's abstract was able to identify differences in the global DNA methylation patterns of psoriatic arthritis (PsA) patients who respond to TNFα inhibitor (TNFi) therapy compared with those who fail to respond. An analysis of genome-wide epigenetic changes revealed 72 and 91 CpG sites of interest in the TNFi-responder group and the TNFi-failure groups, respectively. Top gene candidates identified in patients who responded to TNFi therapy included *TRAPPC9*, *CCR6*, and *PSORSC13*. Top candidate genes in patients failing to respond to TNFi therapy included *CD70* and *TNFRSF1B*. These preliminary results also highlight the possible importance of epigenetic (methylation) changes in the modulation of the TNFα signalling pathway and suggest that the high priority candidate regions and genes identified warrant validation in further studies.

Biologic agents have changed the treatment of many rheumatic diseases, but little is known about their long-term safety profiles. The long-term safety effects of treatment with biologic agents was the subject of Joost F. Swart's abstract, which investigated the safety of drug regimens used to treat juvenile idiopathic arthritis (JIA). The study utilised data from the Pharmachild registry to investigate outcomes in JIA patients treated with either methotrexate (MTX) alone or MTX in combination with one or more biologic agents, with the results suggesting that the introduction of one or more biologic agents sequentially increases the rate of serious adverse events (SAEs) and infections compared with treatment with MTX alone. The incidence rates of SAEs increased with the addition of ≥1 biologic agents and a similar trend was observed for infections. The incidence rates for injury, poisoning, and procedural complications, blood and lymphatic system disorders, and eye disorders were higher in the group treated with more than one biologic agent, whereas the incidence rates for gastrointestinal and hepatobiliary disorders were higher in the MTX-alone group. There was also a greater incidence of drug discontinuation due to adverse events or drug intolerance in the groups receiving biologic agents.

The effect of anti-TNF or disease-modifying anti-rheumatic drug (DMARD) therapies on the work disability (WD) experienced by UK PsA patients was addressed by William Tillett's abstract, which observed a significant improvement in presenteeism (reduced effectiveness at work), productivity loss, and disease activity following initiation with these therapies in a real-world setting. Improvements in WD and disease activity were greater and more rapid among those commenced on anti-TNF compared with those commenced on DMARD therapy. Among those commenced on anti-TNF therapy, presenteeism improved from 40% (interquartile range [IQR]: 20-60) to 10% (IQR: 0-30) and productivity loss improved from 45% (IQR: 26-68) to 10% (IQR: 0-30). Among those commencing DMARD, presenteeism improved from 30% (IQR: 10-60) to 20% (IQR: 10-50) and productivity loss improved from 40% (IQR: 20-70) to 25% (IQR: 10-60). The difference in the change in presenteeism between treatment groups became significant at 2 weeks and was sustained over 24 weeks. There were no significant changes in the level of employment in either treatment group. DAPSA scores improved over 24 weeks from 53 (IQR: 38.3-68.4) to 14 (IQR: 6.9-37.4) in the anti-TNF group, which was defined as a good response according to established cut-off values, and improved from 39 (IQR: 27.9-58.4) to 30 (IQR: 18.4-38.5) in the DMARD group, which was defined as a poor response.

Improvements in WD and disease activity were greater and more rapid among those commenced on anti-TNF compared with those commenced on DMARD therapy.

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Interview with Prof Iain McInnes

Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK.

Q: Could you please tell us a little more about your current research on spondyloarthritis?

A: Well, I have been interested for many years in the pathways that drive spondyloarthritis, and particularly psoriatic arthritis (PsA). PsA is a disease that affects many tissues – skin, joint, and physis – and there are certainly common pathological features that are starting to emerge. We know from genome-wide studies, for example, that the interleukin (IL)-23/IL-17 pathway looks particularly interesting.

Now, for many years, in my laboratory (we are a cellular immunology lab primarily), we have been interested in identifying cells that release IL-17, cells that respond to IL-23, and looking at their functions, and along with many other groups, we have come to the conclusion that the IL-23/IL-17 pathway is really quite a prudent, effective, inflammatory cascade. So, for example, if you look at the tissues of people with PsA in the skin, in the joints, and even actually in circulating peripheral bloods, we find elevated levels of IL-17a expression and tumour necrosis factor (TNF) expression, and that fits with the idea that these might become useful therapeutic targets.

Q: How has the field of rheumatology developed since you first began your medical career?

A: The last decade has seen an unbelievable change in the rheumatology spectrum. When I started my clinical practice, the agents available to me were methotrexate, gold, and penicillamine, and whilst they were moderately effective in some patients, they were very often toxic, and the overall benefits accrued to patients were very modest indeed. Now, starting off with TNF-blocking biologics, we have seen extraordinary changes - it is really so exciting to be a rheumatologist - and the PsA field benefited greatly from the advent of TNF blockade. The problem of course is that TNF blockers are efficacious in perhaps two-thirds of patients, but even in those patients, at over 4 or 5 years, around half the patients will have stopped the medication. So in a lifelong disease, often starting in the early 20s, there is a lot of work to do. So, an exciting decade, but what have we achieved? Well, now we have got new targets, and that is really what has been driving me and many colleagues of late: thinking about how to use the presence and functional biology of IL-23 and IL-17 to move to new therapeutics and new strategies.

Q: With this said, what do you hope to accomplish in the next six months?

A: My personal target for the next 6 months is to translate some of the trial datasets that we have into really easily understood clinical outputs. We are very convinced now that targeting P40 with ustekinumab or IL-17a with secukinumab, for example, leads to clinically meaningful improvements in people with PsA. The next target is to work out how to use these drugs most effectively, and in which patients; are there some who will benefit more from one or another strategic approach? And also to get some familiarity with these agents; how well tolerated are they? Are there going to be adverse events about which we should be concerned? Of course it is early days because they are still relatively new to our practice, but there is a lot of work to do in a relatively short period of time.

Q: What do you think are the main challenges rheumatologists face today?

A: We have been celebrating success, but that would be not to ignore the very great challenges that we still face. So, first of all, we cannot yet cure any of our rheumatic diseases, and if we think particularly about PsA we cannot cure the disease. We are offering young people a lifelong chronic illness for which, yes, we can improve matters, but very often we offer people partial responses and we congratulate ourselves. But actually, what we should really be doing is looking to achieve remission in the majority of our patients, remission that can be maintained potentially without needing chronic drug therapeutics, and we are nowhere near that for the majority of our patients. So the major challenge is to understand why people respond only partially, to understand how to get them to remission, and to understand how to keep them there.

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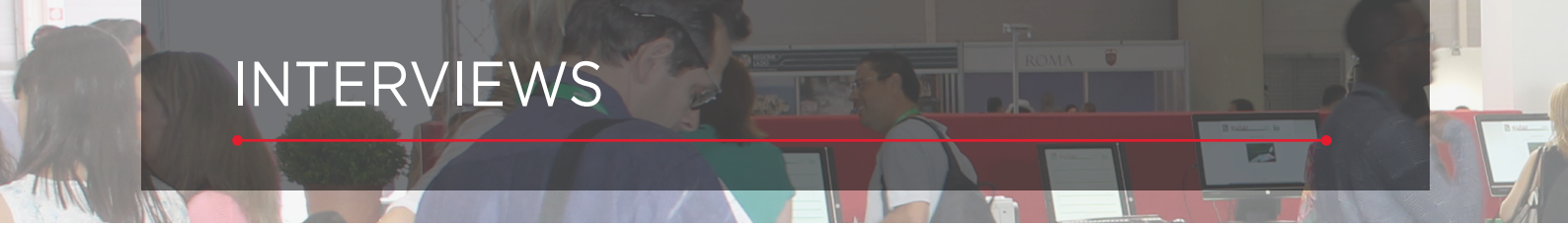


Prodromos Sidiropoulos

Associate Professor of Rheumatology, Head of the Rheumatology Clinic, School of Medicine, University of Crete, Crete, Greece.

Q: Why did you decide to embark on a career in rheumatology? What do you find particularly interesting about this area of medicine?

A: It is an interesting clinical practice, and autoimmunity is a very interesting area of novel knowledge that could provide some promising new therapeutic interventions in this field of medicine. Overall, it is a promising career.

Q: How would you describe the general pace of progress in rheumatology? Should more resources be provided for research?

A: Rheumatology is rather interesting and satisfactory in terms of novel therapies. Nevertheless, despite the significant progress, there are gaps in our knowledge of pathophysiology, prognosis, predictors of response to therapy, and the management of comorbidities that still exist.

Q: To what extent has our knowledge of the pathogenesis of systemic autoimmune diseases increased since you first began researching this topic? How much has this impacted on the treatment of patients with these conditions?

A: Significant progress has been made in this field of disease pathogenesis over the last 15 years (genetics, genomics, immune system homeostasis, etc.). However, the impact of this novel knowledge in terms of new diagnostic and prognostic tests and novel therapies has not been in the same league.

Q: How useful to the field is information obtained from the nationwide registry for the long-term follow-up of patients on biological agents?

A: These are data of great importance because they shed light on everyday clinical practice and real-life experience gained in our country.

Q: How important is it to take into account the side-effect profiles of biological treatments when administering these to patients with autoimmune rheumatic diseases?

A: This is a really important issue because the safety profiles of patients may guide the selection of therapeutic agents in the absence of prognostic markers of response to therapy.

Q: How important is the development of guidelines for clinical practice, which is something you are heavily involved in? To what extent have such guidelines improved patient care?

A: These are 'rules' to homogenise clinical practice and, at the same time, give the freedom of choice to treating physicians. Whether or not their implementation in clinical practice has changed clinical decisions is yet to be determined.

Q: What is the greatest challenge facing rheumatologists over the next few years?

A: To incorporate novel knowledge from basic science and wise application of novel therapies into clinical practice.

Q: How important is the annual EULAR congress for researchers and clinicians working in rheumatology?

A: General rheumatology congresses are of questionable importance.

Q: What advice would you give to young medical professionals starting out on a career in rheumatology?

A: Have the patient at the centre of their practice. Also, ensure continuous updates for new developments in the field.

"These are 'rules' to homogenise clinical practice and, at the same time, give the freedom of choice to treating physicians."

Elaine Dennison

Professor of Musculoskeletal Epidemiology and Honorary Consultant in Rheumatology, MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, UK.

Q: Please give us an overview of your career to date. How did you first become involved in the field of rheumatology, and what led you to the position you currently hold at Southampton General Hospital?

A: I decided upon rheumatology as a career whilst a medical student at Cambridge; having flirted with the idea of neurology, I so enjoyed my rheumatology attachment at Addenbrooke's Hospital (where I saw teamwork at its very best) I decided that this was the career for me. I came to Southampton for a medical rotation in 1992 and have remained in Wessex (bar a 12-month period in New Zealand) ever since. Knowing that laboratory research was not for me, I was very fortunate to meet Cyrus Cooper while I was a senior house officer and successfully applied for a Wellcome Training Fellowship in epidemiology in 1995, which allowed me to train in academic rheumatology. I remain based at the Medical Research Council Lifecourse Epidemiology Unit (MRC LEU) in Southampton.

Q: Tell us a little about your research. What are you currently working on and what do you hope to accomplish in the next year?

A: My particular research interest centres on musculoskeletal ageing, particularly osteoporosis and osteoarthritis. I work largely with a cohort of older men and women born in Hertfordshire and still living there 80 years later (the Hertfordshire Cohort Study). We have plans to initiate a further follow-up study in the coming months, which will look at the interrelationships between muscle and bone ageing, and we hope to also involve their children in our next phase of research. I very much hope that my involvement in the Health Quality Improvement Partnership national audit of inflammatory arthritis will also allow research that will help us improve patient care in the future.

Q: How has the field of rheumatology evolved since you began your medical career? Where do you think is it heading?

A: It has changed enormously. The advent of the biologic therapies has represented a huge advance; it has been wonderful to see the area unfold. As a rheumatologist with a particular interest in osteoporosis, I would also have to mention the advances we have seen in the approach to fragility fracture; we have the ability to identify and treat the patients at highest risk with a wide range of therapies that continues to expand.

Q: What impact does the lifestyle of the average British citizen have on their bones? How does this compare with the rest of Europe and the world?

A: We are aware that regular weight-bearing activity is very important for bone health, as is an adequate dietary calcium intake and sufficient vitamin D through sunlight exposure or supplements. We also know that while some alcohol is beneficial, excess alcohol is detrimental, as is cigarette smoking. Britain is not blessed with the best sunlight record compared with many parts of Europe, so vitamin D insufficiency is quite common, for example. However, in countries where there is a lot of sun, the use of sun block means that vitamin D insufficiency can be common there too!

Q: Is there any disparity in the quality of rheumatological treatment between the UK and the rest of Europe? If so, what can be learned from the British experience?

A: I am not sure I am qualified to judge this as I have not practised in Europe. I would say that I think the standard of care in UK rheumatology is high, but I hope the national audit of inflammatory arthritis led by the British Society of Rheumatology and Northgate in partnership with the MRC LEU will lead to sharing best practice

and improve care for our patients with new inflammatory arthritis. The International Osteoporosis Foundation is very active in promoting pan-European initiatives – Capture the Fracture, looking at benchmarking fracture liaison services, is one example.

Q: What can be done by physicians, governing bodies, and other influencers to promote the improvement of bone health?

A: Education (for doctors and patients, specifically for secondary prevention, and for everyone for primary prevention) and recognition of the importance of the problem by funders – leading to initiatives to reduce the burden, e.g. fracture liaison; the work of the National Osteoporosis Society is so important for this.

Q: In your opinion, how important are events such as the EULAR congress to the field of rheumatology, and why?

A: They are invaluable for the opportunities they provide to learn, share ideas, and network.

Q: What do you think has been the single greatest accomplishment of your medical career?

A: I think one of the moments I felt proudest was when I was awarded the Michael Mason Prize by the British Society of Rheumatology in 2014 in recognition of my research career to date. It was a real honour, especially when I considered previous recipients.

Q: How has the teaching of rheumatology changed since you began your career, and what do you find are the most effective approaches to education in this subject?

A: The single biggest change has probably been the advent of the internet – now we have access to so many web-based events that allow us to access education at a time that suits us, or from events that we cannot physically attend.

Q: What is the biggest challenge facing rheumatologists today, and what do you feel must be done to overcome it?

A: As a rheumatologist with a particular interest in musculoskeletal conditions that are common in later life, I would say the biggest challenge is the demographic shift towards a rapidly ageing population because of the health impact this may have, specifically on osteoporotic fracture and osteoarthritis. I think a combination of primary prevention, centred on public health initiatives, and secondary prevention, such as fracture liaison services, are both required.

Ian C. Chikanza

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

Q: Could you tell us a little about your research and any current projects that you may be working on?

A: My current work at the moment involves looking at the factors that influence responses to anti-tumour necrosis factor (TNF) therapy and trying to identify those patients who are unlikely to respond to anti-TNF therapy, as well as identifying what other biologics they may respond to.

Q: What do you think are the main challenges that face rheumatologists today?

A: I think the cost of drugs is the main challenge because biologics are quite expensive. Also, the targeted oral chemical entities that are coming onto the market are equally expensive, so that is a major challenge. However, the advent of biosimilar biodrugs will ease the financial burden to some extent. This development is welcome, especially for patients in the third world where financial resources are very limited.

Q: How has the field of rheumatology developed since you first began your career?

A: Well I think that rheumatology has been at the forefront of developing biological and targeted treatments, and this was an area in which I was one of the pioneers at Guy's Hospital where

we were the first group to use a biologic in treating rheumatic arthritis (RA). I was the first doctor to administer a biological treatment in an RA patient using an antibody developed jointly by research groups led by Prof Panayi at Guy's Hospital, of which I was a part of, and Prof Janosy at the Royal Free Hospital. This was a mouse anti-CD7 monoclonal antibody. This really heralded the use of targeted biodrugs in the management of rheumatic inflammatory diseases, and the understanding of the physiological pathways involved and the targeting of particular aspects of the inflammatory pathway. This work has really opened up novel ways of treating other diseases where inflammation plays a key role.

Q: Do you see the field heading into new avenues in the future?

A: I think in the future we are going to see more personalised treatment as we understand the physiological mechanisms of inflammation, which appear to be different in different individuals as confirmed by observations that some patients respond differently than others. There will be more chemical molecules, in particular drugs that target the kinin intracellular pathways, and more developments in the potential use of siRNA as targeted therapeutic agents once the intracellular delivery issues are sorted.

Q: In terms of teaching rheumatology, what do you think is the most effective approach when educating others on the subject?

A: I think it is really a mixture of clinical work and practice. As you know, medicine is part science and part art, and the more you practise it the better you will become. It is also an apprenticeship; I foresee a situation whereby trainees are spending more time with more experienced and senior rheumatologists, and honing their skills with regard to how they will approach and manage patients.

Imad Uthman

Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon.

Q: Give us an overview of your medical career to date. How did you get into the field of rheumatology, and what has led you to the position that you currently hold at the American University of Beirut Medical Center?

A: My interest in rheumatology grew after passing a month of elective during my residency in internal medicine. I wanted to become a gastroenterologist but after passing this elective I was fascinated by this specialty. Although no fellowship programme was available at our medical school, I pushed hard to establish one and I was the first fellow to graduate in this specialty.

Afterwards I received the Metro Ogryzlo International Fellowship from the Canadian Arthritis Society, and I joined the rheumatology division at the Notre-Dame Hospital in Montreal, Canada for an additional 2-year fellowship. In 1995 I joined the American University of Beirut Medical Center as an Assistant Professor, and in 2011 I became the division's chief.

Q: Tell us a little about your current line of research; what do you hope to accomplish in the next year?

A: My current research focus is establishing a prospective registry for rheumatoid arthritis and spondyloarthritis patients on biologic therapy. My other research focus is the antiphospholipid syndrome; in fact this is my favourite topic, and I have published a number of manuscripts in this field. My aim is to position our rheumatology unit as a regional centre of excellence for this disease.

Q: How has the field of rheumatology evolved since you began your medical career? Where do you think it is heading?

"The greatest challenge facing rheumatologists in the coming years is the provision of novel therapies..."

A: In fact the field of rheumatology has evolved tremendously since I joined this specialty 20 years ago. In the old days we had few drugs to manage our patients; nowadays and with the introduction of biologic therapies, the whole prospect of treatment of the connective tissue diseases has changed. The future looks quite bright, as the pipeline of research is introducing more effective and potent therapies for the various autoimmune diseases.

Q: What impact does the lifestyle of the average Lebanese citizen have on their bones and joints? How does this compare with Europe and the rest of the world?

A: The lifestyle of the average Lebanese citizen is characterised by relatively more activity as compared to the European population and less obesity as compared to the USA population. This reflects in a lower prevalence of advanced osteoarthritis.

Q: Is there any disparity in the quality of rheumatic treatment between Lebanon and Europe? If so, what can be learnt from the Lebanese experience?

A: I do not think there is any disparity in the quality of rheumatic treatment between Lebanon and Europe. Lebanese patients have access to almost all biologic therapies. The Lebanese Ministry of Health provides full coverage of the cost of these therapies for the Lebanese population who are not covered by private insurances. The problem lies in the Palestinian and Syrian refugee population living in the country, and who account for nearly a quarter of the population of Lebanon currently: these patients have no access to these drugs.

Q: What can be done by physicians, governing bodies, and other influencers to promote the improvement of rheumatic health?

A: Increasing the awareness about rheumatic diseases and the importance of early treatment in the general population and primary care physicians. The role of the rheumatologist is still not very well

defined in the community and many patients with inflammatory rheumatic diseases are unfortunately taken care of by orthopaedic surgeons, therefore a promotion of the role of the rheumatologist is crucial.

Q: In your opinion, how important are events such as the EULAR congress to the field of rheumatology, and why?

A: The EULAR meeting remains the most important international event in the field of rheumatology, as it gathers most of the rheumatology researchers in the world and is a forum where the latest discoveries in the field of rheumatology are presented.

Q: Last year you co-authored a paper for *EMJ Rheumatology* entitled 'Antiphospholipid syndrome novel therapies' – has there been much progress in this area since the publication of this article? Have the novel therapies that you detailed in your paper become more widely used?

A: The results of many studies in the field of treatment of the antiphospholipid syndrome are emerging, and look quite promising especially in the area of new anticoagulant therapies. More prospective studies are still needed before these new drugs are approved as standard therapies for this syndrome.

Q: In your opinion, what will be the greatest challenge facing rheumatologists in the next few years?

A: The greatest challenge facing rheumatologists in the coming years is the provision of novel therapies, namely biologic agents to the majority of patients who need these drugs. The cost of these medications is very high and many patients in developing countries have no access to these drugs.

Q: Of all your accomplishments in rheumatic medicine, which are you most proud of?

A: My biggest pride in the field of rheumatology is that I have promoted this specialty in my country Lebanon, by establishing a rheumatology fellowship at the American University of Beirut Medical Center. This was the first programme of its kind in the country and approximately 20 rheumatologists have graduated from the programme over the last two decades, some of whom are now leading international researchers in the field.

Richard Conway

Department of Rheumatology, Mater Misericordiae University Hospital, and University College Dublin, Dublin, Ireland.

Q: Your recent paper for EMJ on obesity and osteoarthritis recognises the potential damage that obesity can have on a person's body; when did you first begin to recognise this trend and what were the signs that it was becoming a big problem?

A: The impact of obesity on osteoarthritis has been recognised for quite some time now. However, obesity has shifted from an endemic issue to epidemic proportions over recent years, and we have seen a corresponding increase in its relevance to our practice.

Q: Following on from this, how common is it for you to come across this problem in your work?

A: We see conditions to which obesity contributes on a daily basis in our practice.

Q: What do you believe are the best ways to tackle this issue in the future?

A: With our present treatments it is very difficult to treat the end results of the problem. As the old adage says 'prevention is better than cure' and I believe that targeting the factors which contribute to obesity at a societal level will be the most effective intervention.

Q: Are there any other areas of rheumatology that you are particularly interested in and would like to research in the future?

A: My main research focus is in vasculitis and in particular giant cell arteritis. I am currently actively involved in research in these areas.

Q: Do you believe there are any areas of rheumatology that should receive more attention, or that have increased in prominence recently?

A: I think rheumatology as a whole has been somewhat neglected and dismissed. These are conditions which cause huge suffering for patients. Many also have increased risks of long-term health problems and death. Effective intervention has the possibility to reduce this but without sufficient investment in research and service provision this will not be possible.

Q: Have there been any recent breakthroughs in rheumatology that have seriously impacted the way you work?

A: The increasing recognition that many rheumatic diseases target more than just the joints has led us to a more holistic treatment approach. Rheumatoid arthritis for example can have significant effects on a patient's heart, lungs, and indeed psychology, which must not be ignored.

Q: Have you experienced any differences in the hospitals you have worked at in the past, and were there any practises that stood out to you as working particularly well?

A: I have encountered many good things in different institutions. We have large numbers of excellent people doing their very best for the patients under their care. Too often it seems that the insights that these people can provide are ignored due to other priorities.

"I think rheumatology as a whole has been somewhat neglected and dismissed."

Q: What recommendations would you give to any young rheumatologists, just starting out in the field?

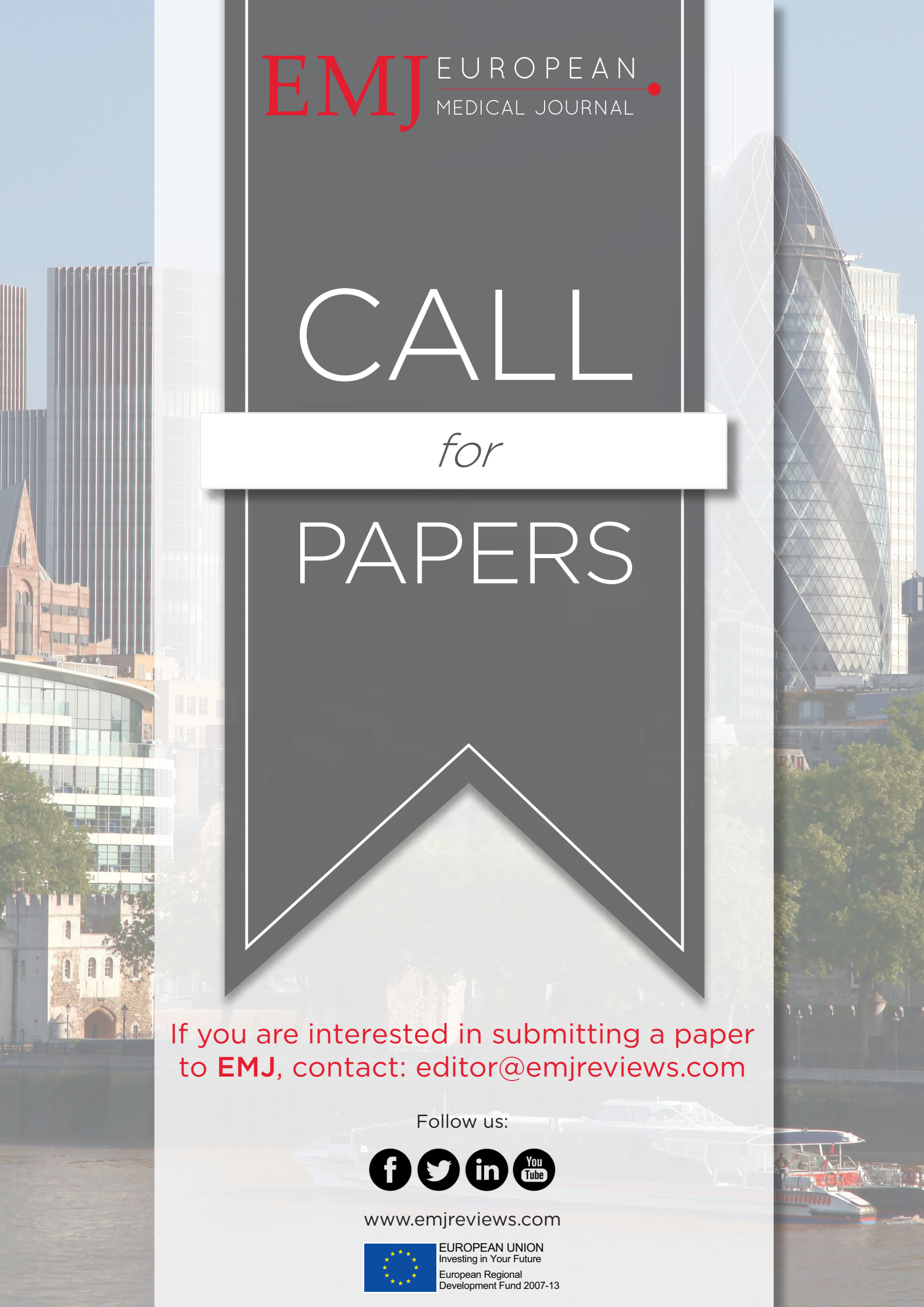
A: You have entered an exciting and rapidly developing area of medicine. There will be many high and low points during your career, and unfortunately very many frustrations. Never forget why you got into rheumatology, and indeed medicine, in the first place. Although you will be forced to spend a lot of time doing other things, our only job is to care for patients.

Q: What drew you towards the field of rheumatology initially?

A: I was attracted to rheumatology as I believed the potential to improve suffering was so significant. At the time I entered rheumatology we were just beginning to see the real impact of effective treatments for inflammatory arthritis. This patient population changed from one characterised by long-term suffering to what was essentially a normal life. That was something I wanted to be a part of.

Q: What have been the highlights of your career thus far?

A: A couple of years ago I worked in an extremely busy clinical service with my colleague and mentor Dr John Carey. Despite the daily demands of our work we used our early mornings and evenings to embark on a series of meta-analyses on aspects of methotrexate use. This project was never going to attract significant support from funding agencies or pharmaceutical companies; however, we believed that there were hugely important questions in relation to patient care and clinical practice that needed to be answered. While it was a major effort to complete this project the results have now been published in important general medical and rheumatology journals. Our findings challenge entrenched beliefs about methotrexate and will change the way it is used in practice.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IL-17 INHIBITION: EMERGING PERSPECTIVES IN THE FUTURE MANAGEMENT OF AXIAL SPONDYLOARTHRITIS

This symposium took place on 12th June 2015 as part of EULAR 2015, the Annual European Congress of Rheumatology representing the official annual meeting of the European League Against Rheumatism (EULAR), in Rome, Italy

Chairperson

Atul Deodhar[1]

Speakers

Dirk Elewaut,[2] Dominique Baeten,[3] Xenofon Baraliakos[4]

1. Oregon Health and Science University, Portland, Oregon, USA
2. Ghent University Hospital, Ghent, Belgium
3. Clinical Immunology and Rheumatology Academic Medical Center/ University of Amsterdam, Amsterdam, Netherlands
4. Rheumazentrum Ruhrgebiet Herne, Ruhr University Bochum, Bochum, Germany

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MEETING SUMMARY

The meeting was opened by Prof Atul Deodhar who introduced the prevalence, epidemiology, and clinical features of axial spondyloarthritis (axSpA), and discussed the ongoing unmet needs in the management of axSpA. Prof Dirk Elewaut described the role of the interleukin-17 (IL-17) pathway in the pathogenesis of axSpA. Prof Dominique Baeten reviewed the latest clinical data from existing and emerging therapies for axSpA. Finally, Prof Xenofon Baraliakos discussed recent advances in the assessment of bone inflammation and structural damage in axSpA. Each discussion was followed by questions and answers. The meeting was concluded with an interactive final discussion between the panellists and the audience, with concluding remarks by Prof Atul Deodhar.

Welcome and Introduction

Professor Atul Deodhar

Low back pain is a highly prevalent condition. In the USA alone, chronic low back pain, defined as a low back pain that persists for >3 months, has been estimated to affect up to 20% of the population at any given time.[1,2] Mechanical back pain accounts for most cases, although back pain can also be inflammatory in nature or due

to other pathologies such as fractures, infection, or tumours.[2] Approximately 15% of patients with long-term inflammatory back pain can develop axSpA, a condition which mainly causes painful inflammation and stiffening of the spine and sacroiliac joints. Patients with inflammatory back pain initially develop non-radiographic axSpA (nr-axSpA), which can (in 10% of cases) progress to ankylosing spondylitis (AS) in which radiographic structural damage is observed over a 2-year period. Although axSpA can remit spontaneously in some patients, it leads to significant disability in others.[2]

In a cross-sectional survey conducted in adults (age range: 20-69 years) as part of the 2009 US National Health and Nutrition Examination Survey (NHANES), 0.55% of the participants reported having received a diagnosis of AS. Based on the European Spondyloarthropathy Study Group (ESSG) criteria, 1.4% of the overall population had axSpA.[3] According to some studies, axSpA may be more common than rheumatoid arthritis (RA),[4-7] and, compared with psoriatic arthritis (PsA) or RA, axSpA has also been shown to be associated with the highest decrease in physical health-related quality of life.[8] In a cross-sectional survey conducted in the USA, patients with AS were more likely, compared with the general population, to be work disabled (13.3% versus 5.7%; p<0.0001) or not to work at all (25.1% versus 21.8%; p=0.07).[9] These associations were stronger among patients with chronic AS (≥20 years) and aged ≥45 years. AS patients were also more likely to have never been married (22.8% versus 15.4%; p<0.0001) or divorced (13.2% versus 10.0%; p=0.02) compared with the general population.

As recommended in the treatment guidelines recently developed by the American College of Rheumatology (ACR) in partnership with the Spondylitis Association of America (SAA) and the Spondyloarthritis Research and Treatment Network (SPARTAN), non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy are the first-line treatment options for patients with axSpA (Ward M et al. Arthritis Rheum in press). Anti-tumour necrosis factor (TNF) α therapy should be given to patients with persistently high disease activity despite conventional treatments.[10] Switching from one TNF inhibitor to another can be recommended in patients with loss of response. However, it should be noted that this recommendation is based on observational data and prospective studies, highlighting the need for further randomised controlled studies to support these recommendations.

Across different studies, approximately 60% of patients with AS treated with anti-TNF therapies (e.g. etanercept, adalimumab, infliximab, golimumab, or certolizumab pegol) achieve the 20% response according to the Assessment in Ankylosing Spondylitis International Society criteria for improvement (ASAS20).[11-15] These observations highlight one of the unmet needs in the treatment of AS, in which up to 40% of patients do not achieve acceptable clinical improvement in their condition. The fact that inhibition of bone proliferation is not maintained (as shown by studies of 2 years' duration), and that the presence of opportunistic infections and other complications may be unacceptable to patients, are among additional limitations associated with the use of anti-TNF therapy. It is therefore important that new therapies are developed for the treatment of axSpA.

IL-17 has a central role in the pathogenesis of SpA.[16-18] IL-17 production is induced during both the innate and adaptive immune responses by a range of different cells, acting on many additional cells and tissues to drive production of further pro-inflammatory cytokines and chemokines, which act in a feedback loop to increase IL-17 production. IL-17 is involved in several pathogenic processes such as inflammation and bone erosion, both of which have been implicated in the development of SpA. In this symposium, the rationale for IL-17 inhibition in axSpA was explored together with the latest advances in treatments for axSpA and the effects of current and emerging treatments on inflammation and structural damage.

Why Target IL-17 in Axial Spondyloarthritis?

Professor Dirk Elewaut

The differentiation of naïve T cells into a variety of T helper (T_H) cells, each with different functions, plays an important role in the adaptive immune system. For instance, T_H1 cells function in cell-mediated immunity against intracellular bacteria and viruses, and are characterised by interferon gamma production, whereas T_H2 cells function in humoural immunity against extracellular parasites, and produce cytokines such as IL-4, IL-5, IL-13, and IL-25, while immunoregulation (peripheral

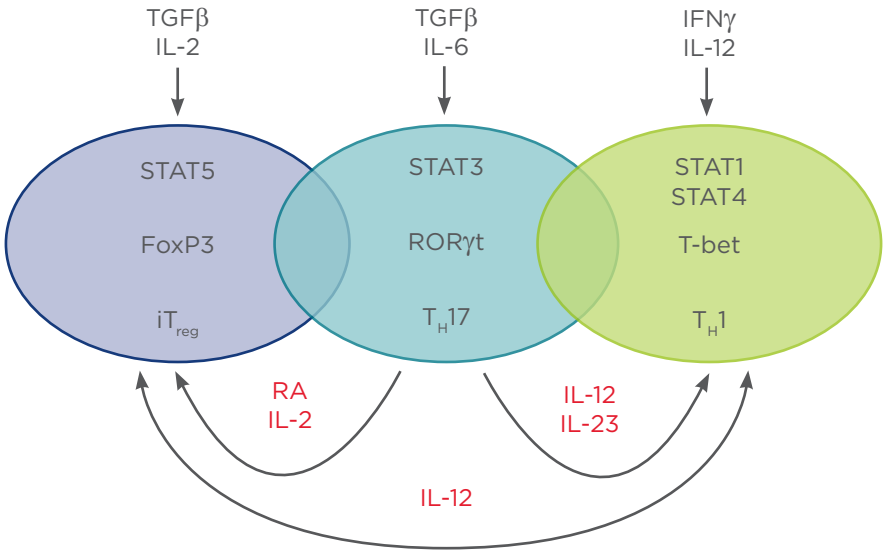
immune tolerance) is mediated by iT_{reg} cells.[19] T_H17 cells also function in cell-mediated immunity but, in contrast to T_H1 cells, they protect against extracellular bacteria and fungi and are characterised by the production of IL-17, as well as IL-22 and IL-26.[19]

Our understanding of the role of IL-23/IL-17 signalling and T_H17 in auto-inflammatory diseases has progressed greatly in the last 20 years, from the initial identification of IL-17 to the recent demonstration of clinical benefits with antibodies against IL-17 and IL-23p19 in psoriasis, AS, RA, and multiple sclerosis.[20] T_H17 cells have been identified as a separate lineage from T_H1 and T_H2 cells. T_H17 differentiation can be driven by transforming growth factor beta (TGFβ) and IL-6 via the IL-17+ lineage-specific transcription factor RORγt, which eventually promotes chronic inflammation and autoimmunity.[21] However, the differentiation of T_H17, iT_{reg}, and T_H1 lineages has been found to overlap, such that early retinoic acid and IL-2 signalling and late IL-23 or IL-12 signalling can deviate T_H17 differentiation towards iT_{reg} and T_H1, respectively (Figure 1). This flexibility in T_H17 levels may have some relevance in inflammatory diseases such as axSpA.[22]

The differentiation, growth, stabilisation, and development of T_H17 effector memory cells involve a range of signalling molecules including IL-1β, IL-6, IL-23, and IL-21. As well as the IL-17 family of cytokines, fully mature T_H17 cells produce IL-21, thus positively feeding back to promote the development of further T_H17 cells. Moreover, T_H17 cells express the chemokine receptor CCR6, which responds to the ligand CCL20 that is present in inflamed joints in axSpA.[21]

IL-17 is not only produced by classical adaptive immunity T_H17 cells in lymphoid organs, but is also produced by cells in several other organs and at sites of inflammation.[20] Natural immunity T_H17 cells in the skin and mucosal tissues express IL-17 in response to IL-1 and IL-23. Group 3 innate lymphoid cells in the gut and skin, and γδT cells in mucosal and peripheral tissues produce IL-17 in response to dectins, IL-1, IL-23, and Toll-like receptor signalling, whereas the γδT cells in the lymphoid organs produce IL-17 in response to IL-1, IL-23, and T-cell receptor signalling. Invariant natural killer (NK) cells in the liver require CD1 and glycolipids to express IL-17.

Susceptibility to AS is largely genetically determined – studies with identical twins estimate heritability to be >90%.[23] The identity of the environmental trigger in most cases of AS is likely to be something very common. The progression of the disease, including the rate of ankylosis, also has a genetic component, with the heritability of radiographic severity estimated at 62%.[24]



The factors identified in red indicate those that deviate the T_H17 developmental programme towards iT_{reg} early (retinoic acid and IL-2) or T_H1 late (IL-23 or IL-12)

Figure 1: Flexibility: Overlap of the T_H17, iT_{reg}, and T_H1 axes of differentiation.
IL: interleukin; TGFβ: transforming growth factor beta; IFNγ: interferon gamma; RA: retinoic acid.

Approximately 25% of the genetic loci involved in the heritability of AS have been identified.[25] Among these, human leukocyte antigen B27 (HLA-B27) accounts for 20% and IL-17 pathway genes around 0.5% of cases.[25] It is thought that these molecules are interconnected, as HLA-B27 is linked to the IL-17 pathway both through NK cell activation[26] and the unfolded protein response (UPR) (Figure 2).[27,28]

Several theories have been proposed to explain the role of HLA-B27 in the pathogenesis of AS. While it is a classical antigen-presentation molecule, there is no strong evidence for an 'arthritogenic' peptide that would be presented to T cells by HLA-B27. Instead, the formation of HLA-B27 heavy chain homodimers on the cell surface may activate IL-17-producing immune cells through NK receptors. Misfolding of HLA-B27 and its subsequent accumulation in the endoplasmic reticulum (ER) may also be involved, leading to a UPR, potentially involving endoplasmic reticulum aminopeptidase 1 (ERAP1), which is also linked to the IL-17 pathway.

Cytokines that upregulate HLA-B27 expression may trigger UPR activation under conditions where HLA-B27 misfolding reaches a critical threshold. This in turn could polarise cells such as macrophages to increase production of IL-23 relative to IL-12. In susceptible individuals with permissive (non-protective) IL-23 receptor genotypes, this may promote T_H17 activation over T_H1, thus inducing IL-17 production and inflammation.[29] It is hypothesised that abnormal innate immune responsiveness to either infection or biomechanical stress can trigger this pathway from HLA-B27 to IL-17.[26] AS may, therefore, be considered an auto-inflammatory disease rather than a strictly autoimmune disease.

Several genetic loci contributing to other rheumatic diseases such as psoriasis and PsA also affect the T_H17 pathway, including IL-23, IL-12, and ERAP1.[30] Indeed, IL-23 and IL-17 can be considered unifying factors in such disorders.[31] IL-23 sensitivity is associated with AS, PsA, and inflammatory bowel disease (IBD), and IL-23 overproduction is associated with SpA (e.g. IL-13 production in psoriasis, HLA-B27 misfolding in IBD, and subclinical ileitis in 70% of SpA patients without IBD).[31]

Evidence is accumulating for the involvement of the IL-17/IL-23 pathway in axSpA, supporting a scenario in which a genetic susceptibility leads to IL-23 overproduction in response to stress and a variety of responsive cells release IL-17-related cytokines that results in the inflammation, osteoproliferation, and skin inflammation seen in spondyloarthritis. IL-23-responsive cells (expressing IL-23 receptor) have been found at the tendon/bone interface in a mouse model, in which overproduction of IL-23 caused periosteal and entheseal pathology similar to that seen in patients with spondyloarthritis.[32] Studies in patients with axSpA and AS have also found increased levels of IL-17-producing cells.[33-35]

In summary, IL-17-producing T_H17 cells in the immune system are involved in inflammatory diseases. Gene polymorphisms in the IL-17 signalling pathway, HLA-B27 misfolding, and IL-17/IL-23 pathways have a role in the pathogenesis of axSpA. There are many cellular sources beyond T_H17 cells that contribute to IL-17 production in spondyloarthritis. In preclinical models of spondyloarthritis, the IL-17/IL-23 pathway mimics clinical spondyloarthritis, including inflammation and bone formation.

Recent Advances in Current and Emerging Treatments

Professor Dominique Baeten

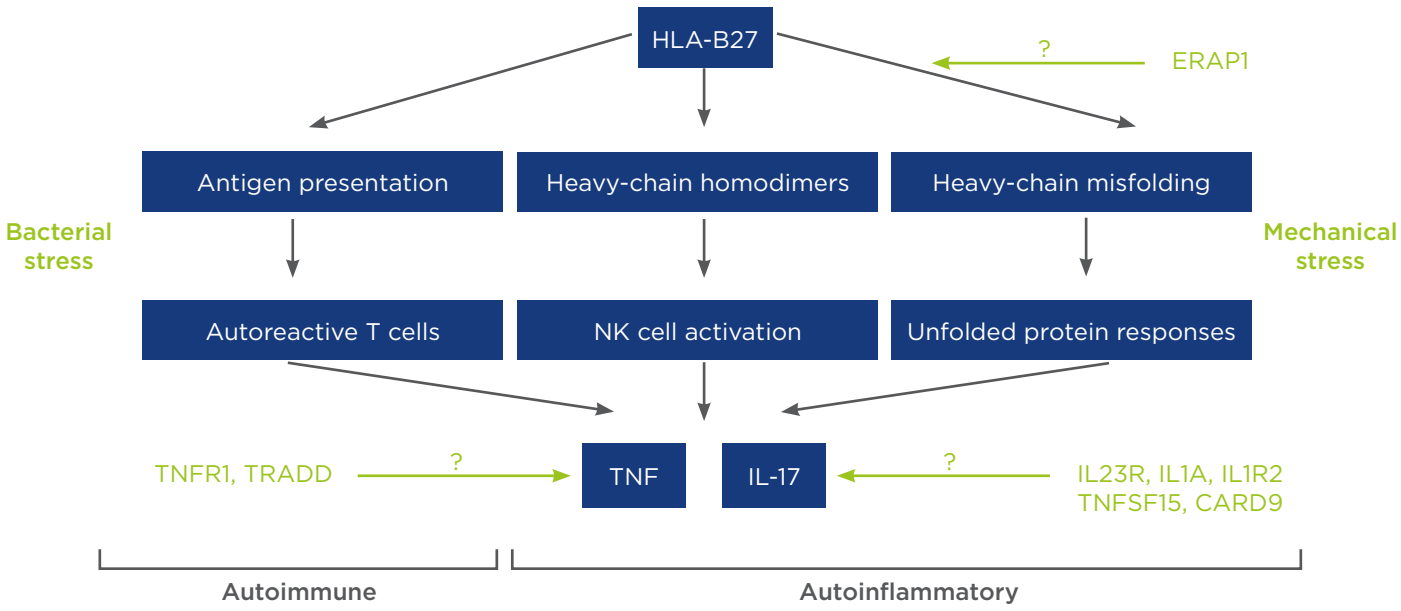
The current standard of care for AS is NSAIDs and local corticosteroid injections as first-line therapy, accompanied by non-pharmacological treatments including education, exercise, physical therapy, rehabilitation, patient associations, and self-help groups. If high disease activity continues, anti-TNF therapy, which has shown good clinical responses in terms of signs and symptoms of inflammation in patients with AS, is the standard second-line treatment.[11-15]

Historically, diagnosis of AS and implementation of therapy were often delayed, in many cases by several years.[36] However, the Assessment of SpondyloArthritis International Society (ASAS) has recently developed new criteria for classification aimed at promoting an earlier and more effective diagnosis and treatment of AS and nr-axSpA (patients with signs and symptoms of axial disease who lack the radiographic damage to the sacroiliac joints to meet the modified New York criteria).[37] As demonstrated in the RAPID-axSpA study, certolizumab pegol was an effective treatment for

patients with AS and those with non-radiographic axSpA.[15] Other trials have shown good responses to anti-TNF therapy in other manifestations of SpA.[38] Patients with AS often present with a range of symptoms, including arthritis, tendinitis, IBD, uveitis, spondylitis, and psoriasis, and it is important that all of these manifestations are treated.

Overall, it is estimated that approximately one-third of patients treated with TNF inhibitors are good responders; another one-third benefit from the treatment but may still experience some signs and symptoms (moderate response); and another one-third are non-responders (or intolerant). Rapid relapse after interruption of treatment, no clear impact on osteoproliferation, and no alternative biologic treatments are among the remaining unmet clinical needs in axSpA.

Abatacept is a fusion protein that selectively binds to CD80 and CD86 receptors on antigen-presenting cells.[39] In this way, abatacept inhibits T cell activation, selectively blocking the specific interaction of CD80/CD86 receptors with CD28 and, therefore, inhibiting T cell proliferation and B cell immunological response. In a prospective, open-label pilot Phase II study conducted to explore the short-term efficacy and safety of abatacept in patients with active AS as an alternative to anti-TNF therapy, no response was observed in TNF inhibitor-naïve patients or patients with inadequate response to TNF inhibitor.[40] No evidence of significant efficacy has also been found with a range of other therapies in Phase II studies in AS, including rituximab (anti-CD20 monoclonal antibody [mAb]), IL-6 and IL-1 blockade, and apremilast (PDE-4 inhibitor), while ustekinumab (IL-12/IL-23 inhibitor) has shown some efficacy in a proof-of-concept study. While there are a number of targets currently under investigation, including IL-17A, new treatment options are urgently required for AS. Secukinumab and ixekizumab are two anti-IL-17 mAbs in clinical development for the treatment of AS, PsA, and/or psoriasis (Table 1). Clinical development of brodalumab, an mAb against IL-17RA, is currently on hold.



'Stress' hypothesis: inflammation is induced by abnormal innate immune responsiveness to mechanical or bacterial danger signals.

AS is an autoinflammatory but not an autoimmune disease.

Figure 2: Potential roles of HLA-B27 in spondyloarthritis.

AS: ankylosing spondyloarthritis; ERAP1: endoplasmic reticulum aminopeptidase 1; HLA-B27: human leukocyte antigen B27; IL: interleukin; NK: natural killer; TNF: tumour necrosis factor; TNFR1: tumour necrosis factor receptor 1; TRADD: tumour necrosis factor receptor 1-associated death-domain protein; TNFSF15: tumour necrosis factor superfamily member 15; CARD9: caspase recruitment domain-containing protein 9.

Table 1: IL-17 blockade in human immune-mediated inflammatory diseases.

Drug	Mechanism	Clinical status
Secukinumab	Fully human anti-IL-17A mAb	Licensed for psoriasis In development for AS and PsA
Ixekizumab	Humanised anti-IL-17A mAb	In development for psoriasis and PsA
Brodalumab	Fully human anti-IL-17RA mAb	Development on hold

AS: ankylosing spondylitis; IL: interleukin; PsA: psoriatic arthritis; mAb: monoclonal antibody.

With two large Phase III trials (MEASURE 1 and MEASURE 2) completed, secukinumab is the anti-IL-17 agent most advanced in its clinical development.[41,42] In this symposium, only the results from MEASURE 1 were discussed. During the MEASURE 1 trial, patients (n=371) were randomised to intravenous (IV) secukinumab 10 mg/kg (Weeks 0, 2, and 4) followed by subcutaneous secukinumab 150 mg or 75 mg every 4 weeks, or matched placebo. Baseline demographics and disease characteristics were well-balanced across treatment groups, and a large proportion of patients were anti-TNF-naïve (approximately 73% in each group).[41]

Significant improvements in the proportion of patients achieving ASAS20 criteria were observed with secukinumab IV-75 mg and IV-150 mg versus placebo after 16 weeks of treatment, with responses sustained through Week 52. At Week 16, ASAS20 response rates were 59.7% and 60.8% with secukinumab IV-75 mg and IV-150 mg, respectively, versus 28.7% with placebo ($p<0.0001$). The onset of response was fast, with most patients responding after 1 or 2 weeks of treatment. During the initial 16 weeks, all predefined primary and secondary endpoints were achieved with both doses of secukinumab. Improvements in ASAS20 response rates at Week 16 with secukinumab versus placebo were observed regardless of prior exposure to anti-TNF agents.[41] Secukinumab also produced rapid and sustained improvements in patient-reported outcomes, including quality of life.[42,43] The efficacy of secukinumab has been also demonstrated in other subtypes of spondyloarthritis.[38]

Secukinumab had a good safety profile in MEASURE 1. The incidence of adverse events was lower in the active treatment groups compared with placebo.[41] Over the entire treatment period, the incidence (number of cases per 100 patient-years) of malignant or unspecified tumours was 0.9 with secukinumab IV-150 mg and 0.4 with secukinumab IV-75 mg versus 2.4 with placebo. Adverse events of interest included *Candida* infections (3 non-serious cases that did not lead to discontinuation) with no signals for invasive infections, neutropaenia (3 cases of Grade 3 and 1 case of Grade 4), and Crohn's disease (3 cases [0.8%; 75 mg] in patients with a history of this disease or with predisposing factors).

In summary, anti-TNF therapies are currently the only biologic therapy for AS. A significant unmet need remains, particularly for patients who have an inadequate response or intolerance to anti-TNF therapy. IL-17A inhibition with secukinumab is effective in patients with AS, with benefits observed regardless of prior anti-TNF exposure. Several outstanding questions remain regarding IL-17 inhibition in AS, including: the long-term efficacy and safety of IL-17 inhibitors; whether they can have an impact on structural damage, and their efficacy in other subtypes of AS; where such agents should be positioned in the AS treatment algorithm in comparison with anti-TNFs; which are the most appropriate patients for treating with IL-17 inhibitors; and whether this is the optimal way to target the IL-23/IL-17 axis or whether other specific targets, such as p40, p19, IL-17A/F, IL-17R, or RORC, would be more effective.

The Imaging Perspective: The Effects of IL-17A Inhibition on Bone Inflammation and Damage

Doctor Xenofon Baraliakos

The natural course of AS, untreated with biologics, shows progression from an initial presentation

of chronic back pain, indistinguishable from any other causes of back pain, to inflammation, bone erosion and, ultimately, ankylosis of the spine over several decades with associated pain and functional disability. During the course of the disease, the structural changes characteristic of AS, such as sacroiliitis[44] and formation of syndesmophytes, can be detected by radiography but by this time it is too late for treatments to halt the progression of the disease.

Over the last 15 years, the use of biologic anti-TNF therapies has been effective in reducing the clinical symptoms of AS, and patients' pain and disability. Magnetic resonance imaging (MRI) of bone oedema to measure inflammation objectively has similarly shown a reduction of inflammation in response to anti-TNF treatments in the long and short-term.[45-47] The effect of anti-TNF therapies on inflammation can potentially have an effect on bone formation in AS. It has been shown that inflammation is linked to new bone formation in the spine in AS,[48] but more recent studies have identified an intermediate stage in which a reduction of inflammatory activity is linked with the development of fatty lesions in subchondral bone marrow.[49] In sites where inflammation had occurred, fatty lesions developed and bone formation was seen more frequently and more rapidly at these sites. Identification of these fatty lesions by MRI could potentially provide an earlier point in the sequence to diagnose and treat progression of AS.

Although anti-TNF therapies such as etanercept, infliximab, and adalimumab have been shown to be effective in reducing the signs and symptoms and improving the quality of life in patients with active AS over 2 years, no significant inhibition of radiographic progression was observed.[50-52] The search for additional treatments is now focussing on other targets in the inflammatory cascade. Successful attempts to treat AS patients have been made with IL-23 and IL-17 inhibition. The preclinical results published by Sherlock et al.[32] in 2012 offer a rationale for the efficacy of this approach. IL-23-responsive cells were identified in a mouse model of enthesitis; these produced IL-17 with subsequent inflammation and tissue damage in response to increased IL-23.[32] This inflammation was reduced by anti-IL-17 treatment.

The potential similarity between the enthesitis model and clinical AS led to a proof-of-concept study of IL-17A inhibition with secukinumab, which included an MRI sub-trial with an open-label extension to investigate whether an imaging response could be observed in addition to a clinical response. The trial showed a rapid clinical response to secukinumab at 28 weeks, which was sustained at 94 weeks. MRI of the vertebral edges showed decreases in inflammation from baseline in the secukinumab arm compared with the placebo arm at 94 weeks. Furthermore, there was no change in the amount of fatty lesions in the patients treated with secukinumab.[53] Structural progression and inflammation were also assessed by MRI imaging in the Phase III MEASURE 1 trial.[41] The Berlin scoring system for bone marrow oedema was used for objective assessment of inflammation. A rapid response in terms of a reduction from baseline in the sacroiliac joint total oedema score was seen in both secukinumab arms at 16 weeks (a change of –1.05 for secukinumab 75 mg and –1.30 for secukinumab 150 mg versus –0.17 for placebo; both $p<0.01$). This was sustained at 52 weeks. A similar response was seen with MRI of the spine at 16 weeks (a change of –2.53 for secukinumab 75 mg and –1.08 for secukinumab 150 mg versus –0.55 for placebo; $p<0.01$ and not significant, respectively). These results confirm that IL-17A inhibition can reduce inflammation in both the spine and sacroiliac joint.[54]

In conclusion, anti-TNF therapies do not inhibit radiographic progression over 2 years of treatment. The IL-17 pathway may play an important role in the pathogenesis of structural damage in AS and thus offers a promising target for new treatments. MRI data demonstrate that IL-17A blockade with secukinumab provides early and sustained reductions in spinal inflammation in both sacroiliac joints and the spine. Further data are required to explore the effects of IL-17 blockade on radiographic progression.

Summary

Axial spondyloarthritis is a relatively common disease that is often poorly managed. Current treatment guidelines recommend NSAIDs as the first-line therapy for axSpA, followed by TNF blockade in patients with high disease activity or with inadequate response. Pharmacological treatments should be accompanied by non-pharmacological therapies that involve education, exercise, physical therapy, rehabilitation, patient associations, and self-help groups. Significant

unmet needs and treatment challenges remain, particularly for patients who have an inadequate response or intolerance to anti-TNF therapy. Opportunistic infections and other complications are among the barriers to providing effective treatment with currently available anti-TNF therapies.

IL-17 has emerged as a central player in the pathogenesis of SpA and thus may be an effective target in axSpA. Promising data are emerging from the use of agents neutralising IL-17 such as secukinumab and ixekizumab. While MRI techniques have demonstrated that IL-17 blockade with secukinumab provides early and sustained reductions in spinal inflammation in both sacroiliac joints and the spine, further data are required to explore the effects of IL-17 blockade on radiographic progression. Finally, several outstanding questions remain regarding IL-17 inhibition in AS, including where such agents should be positioned in the AS treatment algorithm, their impact on structural damage, and whether there is an optimal way to target the IL-23/IL-17 axis.

REFERENCES

1. Perina DG. Mechanical Back Pain: Background, Pathophysiology, Epidemiology. 2015. Available at: http://emedicine.medscape.com/article/822462-overview. Last accessed: 8 July 2015.

2. Baraliakos X, Deodhar A. Unanswered questions in the management of axial spondyloarthritis: an opinion piece. Clin Rheumatol. 2014;33(10):1359-65.

3. Reveille JD et al. The prevalence of HLA-B27 in the US: data from the US National Health and Nutrition Examination Survey, 2009. Arthritis Rheum. 2012;64(5):1407-11.

4. Saraux A et al. Prevalence of spondyloarthropathies in France: 2001. Ann Rheum Dis. 2005;64(10):1431-5.

5. Guillemin F et al. Prevalence of rheumatoid arthritis in France: 2001. Ann Rheum Dis. 2005;64(10):1427-30.

6. Helmick CG et al; National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum. 2008;58(1):15-25.

7. Adomaviciute D et al. Prevalence survey of rheumatoid arthritis and spondyloarthropathy in Lithuania. Scand J Rheumatol. 2008;37(2):113-9.

8. Mease P. Comparing Health-Related Quality of Life across Rheumatoid Arthritis, Psoriatic Arthritis and Axial Spondyloarthritis: Analyses from Certolizumab Pegol Clinical Trial Baseline Data. Ann Rheum Dis. 2013;72(Suppl 3):A766-A7.

9. Ward MM et al. Impact of ankylosing spondylitis on work and family life: comparisons with the US population. Arthritis Rheum. 2008;59(4):497-503.

10. Braun J et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2011;70(6):896-904.

11. Davis JC et al. Recombinant human tumour necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomised, controlled trial. Enbrel Ankylosing Spondylitis Study Group. Arthritis Rheum. 2003;48(11):3230-6.

12. Van der Heijde D et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomised, double-blind, placebo-controlled trial. Arthritis Rheum. 2006;54(7):2136-46.

13. Van der Heijde D et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomised, placebo-controlled trial (ASSERT). Arthritis Rheum. 2005;52(2):582-91.

14. Inman RD et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomised, double-blind, placebo-controlled, phase 3 trial. Arthritis Rheum. 2008;58(11):3402-12.

15. Landewé R et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled phase 3 study. Ann Rheum Dis. 2014;73(1):39-47.

16. Lin AM et al. Mast cells and neutrophils release IL-17 through extracellular trap formation in psoriasis. J Immunol. 2011;187(1):490-500.

17. Nestle FO et al. Psoriasis. N Engl J Med. 2009;361(5):496-509.

18. Res PCM et al. Overrepresentation of IL-17A and IL-22-producing CD8 T cells in lesional skin suggests their involvement in the pathogenesis of psoriasis. PLoS ONE. 2010;5(11):e14108.

19. Di Cesare A et al. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. J Invest Dermatol. 2009;129(6):1339-50.

20. Gaffen SL et al. The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. Nat Rev Immunol. 2014;14(9):585-600.

21. Korn T et al. IL-17 and Th17 Cells. Annu Rev Immunol. 2009;27:485-517.

22. Basu R et al. The Th17 family: flexibility follows function. Immunol Rev. 2013;252(1):89-103.

23. Brown MA et al. Susceptibility to ankylosing spondylitis in twins: the role of genes, HLA, and the environment. Arthritis Rheum. 1997;40(10):1823-8.

24. Brophy S et al. Concordance of disease severity among family members with ankylosing spondylitis? J Rheumatol. 2004;31(9):1775-8.

25. Cortes A et al. Association study of genes related to bone formation and resorption and the extent of radiographic change in ankylosing spondylitis. Ann Rheum Dis. 2015;74(7):1387-93.

26. McMichael A, Bowness P. HLA-B27: natural function and pathogenic role in spondyloarthritis. Arthritis Res. 2002;4 Suppl 3:S153-8.

27. Colbert RA et al. From HLA-B27 to spondyloarthritis: a journey through the ER. Immunol Rev. 2010;233(1):181-202.

28. Dougados M, Baeten D. Spondyloarthritis. Lancet. 2011;377(9783):2127-37.

29. Layh-Schmitt G, Colbert RA. The interleukin-23/interleukin-17 axis in spondyloarthritis. Curr Opin Rheumatol. 2008;20(4):392-7.

30. Hébert HL et al. Genetic susceptibility to psoriasis and psoriatic arthritis: implications for therapy. Br J Dermatol. 2012;166(3):474-82.

31. Cua DJ, Sherlock JP. Autoimmunity's collateral damage: gut microbiota strikes 'back'. Nat Med. 2011;17(9):1055-6.

32. Sherlock JP et al. IL-23 induces spondyloarthropathy by acting on ROR-

γt+ CD3+CD4-CD8- entheseal resident T cells. Nat Med. 2012;18(7):1069-76.

33. Appel H et al. Analysis of IL-17(+) cells in facet joints of patients with spondyloarthritis suggests that the innate immune pathway might be of greater relevance than the Th17-mediated adaptive immune response. Arthritis Res Ther. 2011;13(3):R95.

34. Kenna TJ et al. Enrichment of circulating interleukin-17-secreting interleukin-23 receptor-positive γ/δ T cells in patients with active ankylosing spondylitis. Arthritis Rheum. 2012;64(5):1420-9.

35. Melis L et al. Systemic levels of IL-23 are strongly associated with disease activity in rheumatoid arthritis but not spondyloarthritis. Ann Rheum Dis. 2010;69(3):618-23.

36. Lipton S, Deodhar A. The new ASAS classification criteria for axial and peripheral spondyloarthritis. Int J Clin Rheumatol. 2012;7(6):675-82.

37. Rudwaleit M et al. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? Arthritis Rheum. 2005;52(4):1000-8.

38. Mease PJ. Secukinumab, a human anti–interleukin-17A monoclonal antibody, improves active psoriatic arthritis and inhibits radiographic progression: efficacy and safety data from a phase 3 randomised, multicentre, double-blind, placebo-controlled study. Abstract 953. ACR/ARHP Annual Meeting, 14-19 November 2014.

39. Herrero-Beaumont G et al. Abatacept mechanism of action: concordance with its clinical profile. Reumatol Clin. 2012;8(2):78-83.

40. Song I-H et al. Treatment of active ankylosing spondylitis with abatacept: an open-label, 24-week pilot study. Ann Rheum Dis. 2011;70(6):1108-10.

41. Beaten DL. Secukinumab, a monoclonal antibody to interleukin-17A, significantly improves signs and symptoms of active ankylosing spondylitis: results of a 52-week phase 3 randomised placebo-controlled trial with intravenous loading and subcutaneous maintenance dosing. Abstract 819. ACR/ARHP Annual Meeting, 14-19 November 2014.

42. Sieper J. Secukinumab, a monoclonal antibody to interleukin-17A, significantly improves signs and symptoms of active ankylosing spondylitis: results of a phase 3, randomised, placebo-controlled trial with subcutaneous loading and maintenance dosing. Abstract 536. ACR/ARHP Annual Meeting, 14-19 November 2014.

43. Deodhar AA. Secukinumab, a monoclonal antibody to interleukin-17A, significantly improves physical function and quality of life in subjects with active ankylosing spondylitis: results of a phase 3 randomised, placebo-controlled trial with intravenous loading and subcutaneous maintenance dosing. Abstract 538. ACR/ARHP Annual Meeting, 14-19 November 2014.

44. Sieper J, van der Heijde D. Review: Nonradiographic axial spondyloarthritis: new definition of an old disease? Arthritis Rheum. 2013;65(3):543-51.

45. Braun J et al. Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicentre, randomised, double-blind, placebo-controlled magnetic resonance imaging study. ASSERT Study Group. Arthritis Rheum. 2006;54(5):1646-52.

46. Lambert RG et al. Adalimumab significantly reduces both spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis: a multicentre, randomised, double-blind, placebo-controlled study. Arthritis Rheum. 2007;56(12):4005-14.

47. Baraliakos X et al. Outcome of patients with active ankylosing spondylitis after two years of therapy with etanercept: clinical and magnetic resonance imaging data. Arthritis Rheum. 2005;53(6):856-63.

48. Baraliakos X et al. The relationship between inflammation and new bone formation in patients with ankylosing spondylitis. Arthritis Res Ther. 2008;10(5):R104.

49. Song IH et al. Relationship between active inflammatory lesions in the spine and sacroiliac joints and new development of chronic lesions on whole-body MRI in early axial spondyloarthritis: results of the ESTHER trial at week 48. Ann Rheum Dis. 2011;70(7):1257-63.

50. van de Heijde D et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. Arthritis Res Ther. 2009;11(4):R127.

51. van der Heijde D et al. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. Arthritis Rheum. 2008;58(5):1324-31.

52. van der Heijde D et al. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group. Arthritis Rheum. 2008;58(10):3063-70.

53. Baraliakos XB et al. Long-term inhibition of interleukin (IL)-17A with secukinumab improves clinical symptoms and reduces spinal inflammation as assessed by magnetic resonance imaging in patients with ankylosing spondylitis. Arthritis Rheum. 2012;64(Suppl 10):574.

54. Baraliakos XB et al. Secukinumab reduces sacroiliac joint and spinal inflammation in patients with ankylosing spondylitis: MRI data from a phase 3 randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2015;74(Suppl 2):281.

IL-17 INHIBITION IN SPONDYLOARTHRITIS: A TARGETED APPROACH IN PSORIATIC ARTHRITIS

This symposium took place on 10th June 2015 as part of EULAR 2015, the Annual European Congress of Rheumatology representing the official annual meeting of the European League Against Rheumatism (EULAR), in Rome, Italy

Chairperson

Philip Mease[1]

Speakers

Erik Lubberts,[2] Iain McInnes,[3] Désirée van der Heijde[4]

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MEETING SUMMARY

Prof Philip Mease introduced psoriatic arthritis (PsA) with a particular emphasis on disease symptoms and an update on the status of current disease management. Erik Lubberts described the interleukin (IL)-17 pathway and its role in the pathogenesis of PsA. Prof Iain McInnes reviewed the clinical evidence for the efficacy of IL-17 inhibition in PsA. Prof Désirée van der Heijde brought the symposium to a close with a presentation on the clinical impact of joint structural damage and strategies for its prevention in PsA.

Psoriatic Arthritis: Where Are We In 2015?

Professor Philip Mease

The prevalence of PsA in the United States and Europe ranges from 0.1-0.3% of the total population (depending upon case definition),[1,2] with a comparatively lower prevalence seen in other parts of the world such as China and Argentina.[3,4] Several relatively recent studies of patients with psoriasis show that 20-30% also have PsA.[5-12] In one such population study,[12] following confirmation of psoriasis by a dermatologist, patients were referred to a rheumatologist for evaluation regardless of their musculoskeletal symptoms.

	Peripheral arthritis	Skin and nail disease	Axial disease*	Dactylitis	Enthesitis
NSAIDs	X		X		
Intra-articular steroids	X				
Topicals		X			
Physiotherapy			X		
Psoralen UVA/UVB		X			
DMARDs (MTX, CsA, SSZ, LEF)	X	X			
Biologics (anti-TNF agents)	X	X	X	X	X

Figure 1: Treatments for psoriatic arthritis: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) evidence review.[22]

*Based on data from ankylosing spondylitis trials (used as surrogate for PsA spondylitis).

CsA: cyclosporin A; LEF: leflunomide; MTX: methotrexate; UVA/UVB: ultraviolet A/B; NSAIDs: nonsteroidal anti-inflammatory drugs; SSZ: sulfasalazine; TNF: tumour necrosis factor; PsA: psoriatic arthritis; DMARDs: disease-modifying anti-rheumatic drugs.

Of approximately 1,000 patients found to have psoriasis, 30% were diagnosed with PsA. Furthermore, 41% of those with PsA were not aware that they had the condition, highlighting the importance of identifying such patients. PsA can present in several heterogeneous clinical manifestations including peripheral arthritis, enthesitis, dactylitis, and spondylitis, necessitating a highly patient-centric approach to diagnosis and assessment of the severity of PsA and patient management to ensure that treatment adequately benefits each domain.

CASPAR (Classification Criteria for Psoriatic Arthritis)[13] represents the most current diagnostic criteria for PsA. This system results in high diagnostic specificity and sensitivity (99% and 94%, respectively)[13] and highlights the need to take into account several factors, including musculoskeletal and skin disease elements, in PsA diagnosis. Clinical deformities and damage that result in functional disability are seen in 20% of patients with PsA.[14] Furthermore, after 10 years, 55% of patients will develop deformation of five or more joints.[15] Of those patients diagnosed with early PsA, a quarter have at least one erosion on presentation at the clinic and almost half will develop erosive disease within 2 years of diagnosis.[16] Predictors of long-term development of erosive disease include initial presentation with numerous tender or swollen joints and the presence of digital dactylitis.[17-19]

Delaying diagnosis exacerbates progressive deterioration, with as short as a 6-month delay in consultation potentially leading to detrimental outcomes for the patient.[20] There is also evidence of increased mortality rates in patients with PsA, the causes of which are similar to those for the population as a whole; however, improvements in mortality rates have been shown in recent years, which may be attributed to the availability of more effective treatments.[21] Clearly, improvements in screening and diagnosis are unmet needs within PsA that could be improved through increased awareness of the disease among dermatologists, primary care physicians, and patients.

With regards to availability and efficacy of treatments for PsA, a Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) evidence review[22,23] showed that non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular steroids display some efficacy in patients with mild disease; however, to alleviate symptoms of moderate-to-severe disease, systemic treatments must be used (Figure 1).

Most disease-modifying anti-rheumatic drugs (DMARDs) have been shown to improve symptoms in the joints of patients with PsA, without improving skin manifestations of the disease. Methotrexate, however, has shown some efficacy for both joint and skin symptoms.[24,25] Although there are few studies of methotrexate in PsA, the randomised, placebo-controlled Methotrexate in

Psoriatic Arthritis (MIPA) study[26] showed no significant effect of methotrexate on several composite musculoskeletal indices after 6 months of treatment. Several studies of anti-tumour necrosis factor (TNF) therapies in PsA have shown efficacy in the musculoskeletal domain as well as in the management of skin disease. With regards to other outcomes, anti-TNF treatments have also resulted in statistically significant improvements in enthesitis, dactylitis, physical function, and qualityof life (QoL).[25,27]

Despite the availability of NSAIDs, DMARDS, and anti-TNF therapies, significant unmet needs remain in PsA. Improved methods of assessment of disease activity are needed to reflect clinical outcomes. Additional biomarkers are needed to facilitate this assessment; at present, the use of the inflammation biomarker, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are generally used. However, CRP and ESR are reported as normal in up to 50% of patients with PsA despite the presence of clinically active disease,[28,29] thus limiting their use. Novel markers are therefore needed to aid diagnosis and assessment of disease activity and to predict structural damage. Furthermore, additional measures are needed which enable clinicians to treat to targets such as minimal disease activity or remission. Currently available treatments may have safety and tolerability issues and some patients show a lack of or diminished sustainability of response. Thus, there is a need for new medicines with novel modes of action and different safety and tolerability profiles, which lead to sustained benefits in patients with PsA.

Treatments for rheumatoid arthritis (RA) have been investigated in patients with PsA; amongst these, IL-1 inhibitors, rituximab, abatacept, the IL-6 receptor inhibitor tocilizumab, and the Janus kinase (JAK) inhibitor tofacitinib are still being evaluated, but have shown some degree of efficacy for PsA.[25,30] Recently-approved treatments for PsA include the IL-12/23 inhibitor ustekinumab and the phosphodiesterase 4 (PDE-4) inhibitor, apremilast.

Novel treatments currently under investigation in patients with PsA include secukinumab and ixekizumab, which are direct IL-17 inhibitors. Treatments are also in development to target IL-23, which is involved in stimulation of T_H17 cell differentiation and activation. Inhibitors of IL-23 include guselkumab, tildrakizumab, and BI655066, which are being assessed for psoriasis, PsA, and ankylosing spondylitis. In addition, several dual inhibitors of IL-17 and TNF are also in development for PsA.[25,30]

Understanding the Pathophysiology of Psoriatic Arthritis: The Role of IL-17

Doctor Erik Lubberts

IL-17A is the key effector pro-inflammatory cytokine in the IL-17 family; it can exist as a homodimer or as a heterodimer complexed with IL-17F. Receptor binding (IL-17 receptor A [IL-17RA]/IL-17RC) results in conformational changes, nuclear factor (NF)-κB activation, and increased transcription of growth factors and cytokines including IL-6/IL-8.[31] IL-17 is produced by T_H17 cells, a novel T helper cell subset, which differentiate from naïve T cells in the presence of polarising cytokines (IL-1 and IL-23 are important in this role for humans).[32] T_H17 cells are also known to produce IL-17F and IL-22. T_H17 cytokines are required for defence against extracellular pathogens such as fungal infections; however, they have also been implicated in cell-mediated inflammation and autoimmune diseases.[32] In addition to T_H17 cells, IL-17A is also produced by multiple lineages of the innate immune system, including mast cells, neutrophils, dendritic cells, γδT cells, macrophages, and natural killer cells.[32] IL-17R signalling has been suggested as a critical pathway in the transition of acute synovitis into chronic destructive arthritis,[33] potentially driven by an IL-17-induced pro-inflammatory feedback loop as a result of an increase in IL-17/TNFα-producing T_H17 cells in peripheral blood in early RA. Further work is warranted to determine whether targeting IL-17 in addition to TNFα may result in neutralisation of T_H17 activity.[34-36]

Evidence for elevated IL-17A/IL-17R signalling in PsA has been demonstrated by several studies. Huffmeier et al. showed that susceptibility to PsA is associated with single nucleotide polymorphisms in *TRAF3IP2* (*ACT1*), which encodes a molecule downstream of the IL-17RA. Elevated IL-23p19/IL-23R and IL-17A/IL-17R expression in psoriatic skin and synovial fluid from patients with PsA,[37-40] as well as increased frequencies of IL-17$^+$ and IL-22$^+$ CD4$^+$ T cells in the peripheral blood of patients with psoriasis and PsA,[41] have been observed. In the synovial membranes of patients with PsA, CD4$^+$ T cells predominate over CD8$^+$

cells, whilst $CD8^+$ cells predominate over $CD4^+$ cells in the synovial fluid of these patients.[42,43] Furthermore, Menon et al.[44] demonstrated a previously unrecognised contribution of $IL\text{-}17^+/CD8^+$ T cells to the pathogenesis of PsA, with levels of these cells showing a correlation with disease activity and radiographic erosion in patients with PsA.[44] These pathways are also thought to contribute to skin inflammation and enthesis, with IL-17 and IL-22 acting via $IL\text{-}23R^+$ resident/IL-23-responsive T cells.[45]

Long-term joint inflammation results in bone erosion in 67% of patients with PsA; however, evidence of new bone formation is also characteristic of PsA, in the form of syndesmophytes, enthesophytes, and the presence of ankyloses (peripheral bony fusion).[14,46] In addition, IL-17 is a potent stimulator of osteoclastogenesis;[47] degradation of Type I collagen in synovium and bone by IL-17 has been demonstrated,[48] and IL-17 in combination with TNFα increases osteoclastic resorption *in vitro*.[49] Potential pathways involved in the formation of bone include the Wnt signalling pathway, the transforming growth factor-beta/bone morphogenic protein pathway, the prostaglandin E2 pathway, and perhaps the balance between IL-23, IL-17, and IL-22.[50,51]

In summary, IL-17A represents the main effector cytokine within the IL-17 family. Elevated levels are found in the skin and synovium of patients with PsA, identifying this as a key cytokine involved in the pathophysiology of skin inflammation, psoriasis, and PsA. IL-17 is involved in the perpetuation of a pro-inflammatory feedback loop between T cells and synovial fibroblasts that may lead to persistent synovitis, and has been shown to be involved in enthesitis and, to some extent, osteoclastogenesis and bone erosion in patients with PsA. The role played by IL-17 in bone formation in these patients is evolving.

IL-17 Inhibition in Psoriatic Arthritis: Current Evidence and Future Perspectives

Professor Iain McInnes

PsA is a heterogeneous disease with a variety of clinical manifestations, which include uveitis, enthesitis, synovitis, osteitis, and disease of the skin and nails. In order for the immune system response to result in such a range of outcomes, the extent of this response must be context-dependent. Consequently, a very different immune response is seen in the gut to that seen in the skin and in the eye, for example. Therefore, when considering clinical evidence for the use of interventional treatments for PsA, expectations of the same magnitude of response in different tissues may not be met, despite the affected tissues having the same underlying pathogenesis.

Publication of new guidelines for the treatment of PsA is imminent; however, currently, the treatment pathway for PsA is to start with methotrexate or another DMARD, before moving to an anti-TNF treatment in patients with persistently high disease activity. Ustekinumab, an anti-IL-23 antibody, is an option in patients who fail to respond or are intolerant of anti-TNF treatments. Several new treatment options are also in development for PsA, including inhibitors of IL-17 and inhibitors of JAK (Figure 2);[52-54] however, it is currently unclear how these will fit into the traditional treatment paradigm for this disease.

The pivotal Phase III trials with the anti-TNF biologics adalimumab,[55] etanercept,[56] infliximab,[57] golimumab,[58] and certolizumab pegol[59] have shown that 50-60% of patients with PsA achieve an American College of Rheumatology 20% improvement criteria (ACR20) response, demonstrating significant long-term improvements in this and associated endpoints including skin symptoms, physical function, and QoL. Registry data show that around half of patients stay on anti-TNF therapy for around 5 years,[60] and these studies reveal a well-established safety profile in PsA in addition to significant long-term improvements in ACR20 responses and radiographic endpoints. Anti-TNF treatment has been associated with an increased risk of infection. In addition, intolerance to treatment or an inadequate response has been observed in some patients together with decreasing drug survival rates with long-term therapy.

Several other novel drugs have been investigated in PsA; these include apremilast which is a PDE-4 inhibitor currently approved for the treatment of PsA. Following 16 weeks of treatment with apremilast, 40% of patients achieved an ACR20 response. In addition, apremilast was shown to be well-tolerated, and continued dosing to Week 24 maintained or further improved the signs and symptoms of PsA.[61]

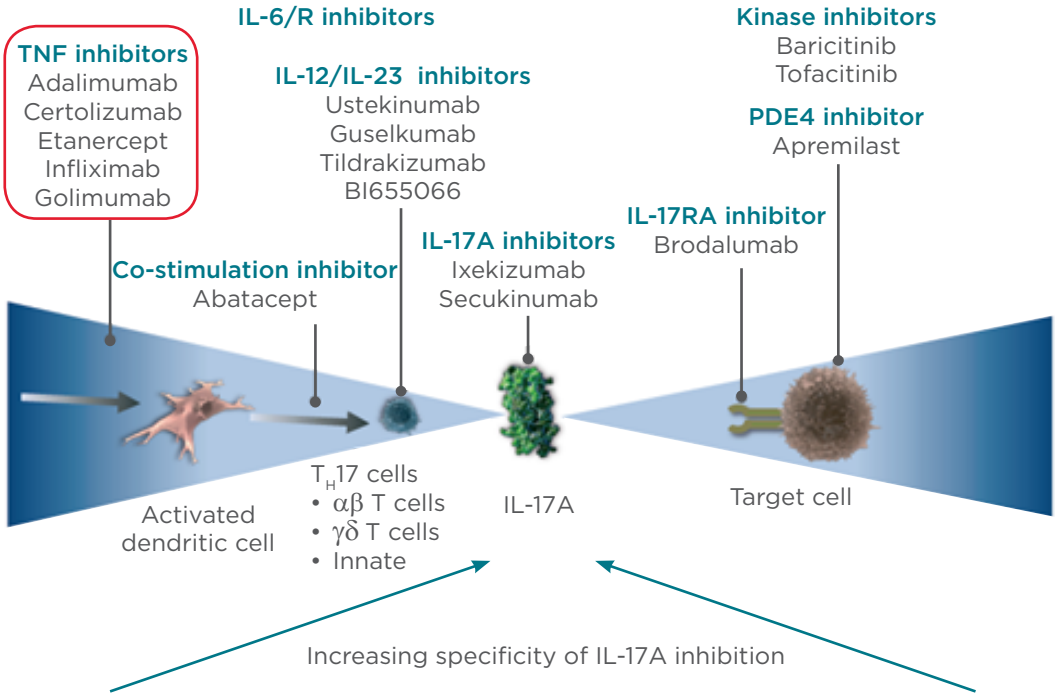

Figure 2: Pathogenesis-driven treatment for psoriatic arthritis.
PDE4: phosphodiesterase Type 4; T_H17: T helper 17 cell; IL: interleukin; TNF: tumour necrosis factor.

Targeting IL-6 has resulted in little response in the skin, although a single Phase II study has shown provisional efficacy in the articular domain. Of the treatments targeting IL-12/IL-23 (ustekinumab, guselkumab, toldrakizumab, BI655066), data are only publicly available for ustekinumab, which is approved for the treatment of PsA. Data from the PSUMMIT Phase III clinical study of ustekinumab in anti-TNF-naïve patients (PSUMMIT I) or those who had previously received treatment (PSUMMIT 2; one-third of participants were anti-TNF-experienced) showed that just under 50% of participants achieved an ACR20 response.[62,63] Although the PSUMMIT 2 study was not designed to compare anti-TNF-experienced/naïve patients, treatment with ustekinumab was effective in patients who were inadequate responders to anti-TNF therapy, although the response was lower than that seen in patients who were anti-TNF-naïve. In addition, ustekinumab was shown to improve enthesitis and dactylitis.[62,64]

Direct targeting of IL-17 has been shown to be an effective treatment for psoriasis. In the Phase III FIXTURE study, greater efficacy was seen with secukinumab, an anti-IL-17A antibody, versus etanercept over a period of 52 weeks in patients with moderate-to-severe plaque psoriasis. Both 150 mgand 300 mg doses of secukinumab resulted in rapid and sustained responses in terms of the co-primary endpoints (a 75% reduction in the mean psoriasis area-and-severity index [PASI] score [PASI 75] and the Investigator's Global Assessment 2011 modified version [IGA mod 2011]), which were significantly higher than those seen for etanercept or placebo.[65] In the Phase III CLEAR study, secukinumab showed greater efficacy versus ustekinumab in both PASI 90 and PASI 100.[66]

Consequently, secukinumab has also been investigated in patients with PsA. FUTURE 1 and FUTURE 2 were randomised, placebo-controlled, multicentre Phase III studies designed to assess the efficacy and safety of secukinumab in patients with active PsA compared with placebo. FUTURE 1 used intravenous administration of secukinumab (10 mg/kg) for 24 weeks followed by subcutaneous administration of a maintenance dose (75 or 150 mg) during the 2-year follow-up phase of the study. This was in contrast to the study design of FUTURE 2, in which subcutaneous secukinumab (75, 150, or 300 mg) was administered over 24 weeks followed by a 5-year follow-up phase using the same doses. For both FUTURE 1 and FUTURE 2, secukinumab significantly improved the ACR20 response after 24 weeks,[67,68] with approximately half of patients in each study achieving ACR20. Of note in FUTURE 2 was the

inclusion of a 300 mg dose of secukinumab which gave a similar response to the 150 mg group.[67,68] In FUTURE 2, when patients were stratified by prior anti-TNF treatment, secukinumab showed clear efficacy irrespective of whether patients were anti-TNF-naïve or inadequate responders to anti-TNF therapy (ACR20 responders: anti-TNF-naïve 58.2% [p<0.0001], 63.5% [p<0.0001], and 36.9% [p<0.01] versus 15.9% [secukinumab 300 mg, 150 mg, and 75 mg versus placebo, respectively]; anti-TNF inadequate responders 45.5% [p<0.01], 29.7% [not significant (ns)], and 14.7% (ns) versus 14.3% [secukinumab 300 mg, 150 mg, and 75 mg versus placebo, respectively]).[68] Similarly, the FUTURE 2 study demonstrated that efficacy was seen with or without concomitant use of methotrexate (ACR20 responders: co-treatment with methotrexate 54.4% [p<0.001], 47.7% [p<0.01], and 44.7% [p<0.05] versus 20.0% [secukinumab 300 mg; 150 mg; and 75 mg versus placebo respectively]; no methotrexate treatment 53.6% [p<0.0001], 53.6% [p<0.0001], and 15.4% (ns) versus 10.4% [secukinumab 300 mg, 150 mg, and 75 mg versus placebo, respectively]).[68] Higher percentages of patients showed improvements in resolution of both dactylitis and enthesitis with secukinumab versus placebo: 56.5% (p<0.01), 50.0% (p<0.01), and 30.3% (ns) versus 14.8% for dactylitis; and 48.2% (p<0.01), 42.2% (p<0.05), and 32.4% (ns) versus 21.5% for enthesitis (secukinumab 300 mg, 150 mg, and 75 mg versus placebo, respectively, at Week 24).[68] With regards to physical function, in both FUTURE 1 and FUTURE 2 rapid improvements were seen in Health Assessment Questionnaire Disability Index (HAQ-DI) with secukinumab (150 mg and 75 mg in FUTURE 1, and 300 mg and 150 mg in FUTURE 2) versus placebo.[67,68]

Secukinumab demonstrated a good safety and tolerability profile in a pooled analysis of the FUTURE 1 and 2 studies.[67,68] The most common adverse events (AEs) for both secukinumab and placebo were nasopharyngitis, upper respiratory tract infections, and headache. The incidence of serious adverse events (SAEs) including inflammatory bowel/Crohn's disease, *Candida* infections, neutropaenia, major adverse cardiac events, and malignancy was low with secukinumab. Overall exposure-adjusted AE/SAE incidence rates across the entire safety period (mean/maximum exposure: 358.1/721 days for secukinumab and 128.6/233 days for placebo) were 210.3/9.0 and 319.6/13.6 per 100 patient-years with secukinumab and placebo, respectively.[69]

In summary, TNF inhibitors have improved outcomes for patients with PsA; however, a significant unmet need remains, particularly for patients who have an inadequate response or intolerance to anti-TNF therapy. Treatment with the PDE-4 inhibitor apremilast or the IL-12/IL-23 inhibitor ustekinumab has shown efficacy in patients with PsA, offering novel therapeutic options. In addition, inhibition of IL-17A with secukinumab has shown significant efficacy in psoriasis and PsA in Phase III trials, and may offer a promising new approach.

Recent Advances in Joint Structural Damage Assessment in Psoriatic Arthritis

Professor Dr Désirée van der Heijde

Structural damage due to PsA is highly prevalent and can occur early in the disease course, with 30-50% of patients presenting with erosions to joints after 2 years[70] and 35-75% of patients in established hospital cohorts showing erosions.[15,71] Joint damage is progressive and increases with duration of the disease.[72] PsA results in bone resorption as well as bone formation and these processes can occur in the same patient, with erosion clearly visible alongside periostitis due to bone formation. Bone erosions resulting from PsA are more destructive than those seen in RA and, ultimately, can result in loss of integrity of the entire joint. Structural damage takes several forms, from shortening of fingers to complete ankyloses of joints.

Several methods of radiological scoring have been developed and validated for damage assessment. The four main methods described (PsA Steinbrocker [Toronto]; PsA Ratingen Score; PsA Sharp method; PsA Sharp/van der Heijde [mTSS]) were all originally developed and tested in patients with RA and adapted for use in PsA. The addition of distal interphalangeal joints (DIPs) of the hands as a scoring site to these methods may be relevant for PsA alongside scoring of new bone formation, pencil-in-cup deformities, and gross osteolysis (GO).[73]

The IMPACT 2 study describes results from two readers making assessments of the number of joints with pencil-in-cup deformities arising in patients after 24 weeks of treatment with the TNF inhibitor infliximab versus placebo.[73] Overall,

few joints showed pencil-in-cup deformities and neither reader reported increases in the incidence of this deformity type over the length of the study in any of the treatment groups. There were also no new joints with GO over the trial period. Evidently, new joints with pencil-in-cup deformations and GO do not occur frequently enough to be used as outcome measures in PsA clinical trials with a length of 24 weeks. In addition, the inclusion of DIPs of the hands to the scoring system does not improve its sensitivity, but are still included because of the frequent involvement in PsA.[73,74]

With regards to other treatments, the effect of a number of anti-TNF therapies on structural damage in patients with PsA has been assessed. Following treatment with five different anti-TNF therapies over 24 weeks, very little change from baseline in mTSS was seen, in contrast to an increase from baseline seen with placebo over the same period. These results were sustained over 52 weeks. A systematic review and meta-analysis of the five randomised controlled trials[75] showed a greater proportion of patients with no radiographic progression at Week 24 (84.5% versus 68.8% for anti-TNF and placebo, respectively), with an odds ratio for progression of 2.7 (anti-TNF treatment versus placebo). In addition, no difference in efficacy was seen among anti-TNF treatments.[75] With regards to the effect of methotrexate on radiographic progression in patients with PsA, data from placebo-controlled studies have yet to be published. Similarly, data are lacking to assess methotrexate versus anti-TNF treatment versus the combination: methotrexate + anti-TNF treatment. Data to assess the effect of methotrexate + anti-TNF therapy are limited and restricted to post-hoc analyses from randomised studies of anti-TNF therapies; hence no additive effect of co-medication with methotrexate and anti-TNF treatment has been demonstrated.[75]

A preplanned, integrated analysis of combined radiographic data from the PSUMMIT 1 and PSUMMIT 2 Phase III, randomised controlled trials of ustekinumab versus placebo was carried out in patients with active PsA.[76] Overall, treatment with ustekinumab resulted in a significantly lower change from baseline in mTSS than placebo.[76] Data from the Phase III FUTURE I study of secukinumab versus placebo in patients with PsA showed significantly less radiographic progression for secukinumab 150 and 300 mg doses versus placebo at Week 24 as assessed by mTSS, a significantly lower change from baseline in erosion score for both secukinumab doses versus placebo, and a significantly lower change from baseline in joint space narrowing score for the intravenous 75 mg secukinumab group. The inhibition of mTSS over 24 weeks was seen irrespective of prior use of anti-TNF treatments.[77] In addition, the mean change from baseline in mTSS was lower for secukinumab versus placebo irrespective of concomitant methotrexate use.[77] Secukinumab demonstrated sustained inhibition of radiographic progression through Week 52.[77]

As seen for RA, preventing the progression of structural damage in order to limit irreversible damage and disability is pertinent for PsA.[78] Hence, EULAR guidelines state that the primary goal of treatment for patients with PsA is to maximise long-term, health-related QoL through control of symptoms, prevention of structural damage, normalisation of function, and social participation; abrogation of inflammation is an important component in achieving these goals.[79] In addition, if patients are seen later in the course of their disease then they are likely to have a higher rate of structural damage.[80] With regards to treatment targets for PsA, clinical remission and inactive disease are important, taking into consideration extra-articular manifestations.[81] It is apparent that structural damage is frequently observed in patients with PsA, which can often have a major impact on function, QoL, and mortality. Treatment with anti-TNF treatments, ustekinumab or secukinumab, can lead to inhibition of the progression of structural damage for these patients.

Summary

In the current treatment pathway for patients with PsA, methotrexate (or an alternative DMARD) is used for initial treatment. When further therapy is required, anti-TNF treatments have demonstrated efficacy in patients with PsA and have also been shown to inhibit structural damage. However, for those patients who show an inadequate response or intolerance to anti-TNF treatments, alternative treatment options are limited.

Novel biologic treatments have demonstrated efficacy in patients with PsA, including the PDE-4 inhibitor apremilast and the IL-12/IL-23 inhibitor ustekinumab. The pro-inflammatory cytokine IL-17 has been shown to play a key role in the pathophysiology of skin inflammation and psoriasis, and is also strongly implicated in synovitis,

enthesitis, and bone erosion in PsA.IL-17 inhibition has demonstrated encouraging results, with the IL-17A inhibitor secukinumab showing superior efficacy versus etanercept (an immunosuppressive human TNF receptor/p75 Fc fusion protein) and versus ustekinumab in psoriasis, as well as significant efficacy versus placebo in PsA. In addition, treatment with secukinumab has been shown to slow the progression of structural deterioration in patients with PsA. As the development of biologic treatmentsfor PsA continues, it remains to be seen how these novel treatment options fit into the traditional treatment paradigm for this disease.

REFERENCES

1. Andrianakos A et al. Prevalence and management of rheumatoid arthritis in the general population of Greece--the ESORDIG study. Rheumatology (Oxford). 2006;45(12):1549-54.

2. Madland TM et al. Prevalence, disease manifestations, and treatment of psoriatic arthritis in Western Norway. J Rheumatol. 2005;32(10):1918-22.

3. Li R et al. Epidemiology of eight common rheumatic diseases in China: a large-scale cross-sectional survey in Beijing. Rheumatology (Oxford). 2012;51(4):721-9.

4. Soriano ER et al. Incidence and prevalence of psoriatic arthritis in Buenos Aires, Argentina: a 6-year health management organization-based study. Rheumatology (Oxford). 2011;50(4): 729-34.

5. Shbeeb M et al. The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982-1991. J Rheumatol. 2000;27(5):1247-50.

6. Brockbank JE et al. Psoriatic arthritis (PsA) is common among patients with psoriasis and family medical clinic attendees. Arthritis Rheum. 2001;44(Suppl 9):S94.

7. Alenius GM et al. Inflammatory joint manifestations are prevalent in psoriasis: prevalence study of joint and axial involvement in psoriatic patients, and evaluation of a psoriatic and arthritic questionnaire. J Rheumatol. 2002;29(12):2577-82.

8. Zachariae H et al. Quality of life and prevalence of arthritis reported by 5,795 members of the Nordic Psoriasis Associations. Data from the Nordic Quality of Life Study. Acta Derm Venereol. 2002;82(2):108-13.

9. Reich K et al. Epidemiology and clinical pattern of psoriatic arthritis in Germany: a prospective interdisciplinary epidemiological study of 1511 patients with plaque-type psoriasis. Br J Dermatol. 2009;160(5):1040-7.

10. Haroon M et al. High prevalence of psoriatic arthritis in patients with severe psoriasis with suboptimal performance of screening questionnaires. Ann Rheum Dis. 2013;72(5):736-40.

11. Walsh JA et al. Limitations in screening instruments for psoriatic arthritis: a comparison of instruments in patients with psoriasis. J Rheumatol. 2013;40(3):287-93.

12. Mease PJ et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. J Am Acad Dermatol. 2013;69(5):729-35.

13. Taylor W et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54(8):2665-73.

14. Gladman DD et al. Psoriatic arthritis (PSA)--an analysis of 220 patients. Q J Med. 1987;62(238):127-41.

15. Gladman DD. Natural history of psoriatic arthritis. Baillieres Clin Rheumatol. 1994;8(2):379-94.

16. Kane D et al. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. Rheumatology (Oxford). 2003;42(12):1460-8.

17. Bond SJ et al. Predictors for radiological damage in psoriatic arthritis: results from a single centre. Ann Rheum Dis. 2007;66(3):370-6.

18. Cresswell L et al. Inflammation in an individual joint predicts damage to that joint in psoriatic arthritis. Ann Rheum Dis. 2011;70(2):305-8.

19. Brockbank JE et al. Dactylitis in psoriatic arthritis: a marker for disease severity? Ann Rheum Dis. 2005;64(2): 188-90.

20. Haroon M et al. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. Ann Rheum Dis. 2015;74(6):1045-50.

21. Ali Y et al. Improved survival in psoriatic arthritis with calendar time. Arthritis Rheum. 2007;56(8):2708-14.

22. Kavanaugh AF, Ritchlin CT; GRAPPA Treatment Guideline Committee. Systematic review of treatments for psoriatic arthritis: an evidence based approach and basis for treatment guidelines. J Rheumatol. 2006;33(7): 1417-21.

23. Cassell S, Kavanaugh AF. Therapies for psoriatic nail disease. A systematic review. J Rheumatol. 2006;33(7):1452-6.

24. Ash Z et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis. 2012;71(3):319-26.

25. Mease PJ. Psoriatic arthritis: update on pathophysiology, assessment and management. Ann Rheum Dis. 2011;70 Suppl 1:i77-84.

26. Kingsley GH et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. Rheumatology (Oxford). 2012;51(8):1368-77.

27. Mease PJ. Measures of psoriatic arthritis: Tender and Swollen Joint Assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S64-85.

28. Punzi L et al. Laboratory findings in psoriatic arthritis. Reumatismo. 2007;59 Suppl 1:52-5.

29. Gladman DD et al. Clinical indicators of progression in psoriatic arthritis: multivariate relative risk model. J Rheumatol. 1995;22(4):675-9.

30. Mease P. Psoriatic arthritis and spondyloarthritis assessment and management update. Curr Opin Rheumatol. 2013;25(3):287-96.

31. Miossec P, Kolls JK. Targeting IL-17 and Th17 cells in chronic inflammation. Nat Rev Drug Discov. 2012;11(10):763-76.

32. Patel DD et al. Effect of IL-17A blockade with secukinumab in autoimmune diseases. Ann Rheum Dis. 2013;72 Suppl 2:ii116-23.

33. Lubberts E. IL-17/Th17 targeting: on the road to prevent chronic destructive arthritis? Cytokine. 2008;41(2):84-91.

34. Tarner IH et al. Emerging targets of biological therapies for rheumatoid arthritis. Nat Clin Pract Rheumatol. 2007;3(6):336-45.

35. van Hamburg JP et al. Th17 cells, but not Th1 cells, from patients with early rheumatoid arthritis are potent inducers of matrix metalloproteinases and proinflammatory cytokines upon synovial fibroblast interaction, including autocrine interleukin-17A production. Arthritis Rheum. 2011;63(1):73-83.

36. van Hamburg JP et al. TNF blockade requires 1,25(OH)2D3 to control human Th17-mediated synovial inflammation. Ann Rheum Dis. 2012;71(4):606-12.

37. Raychaudhuri SP et al. IL-17 receptor and its functional significance in psoriatic arthritis. Mol Cell Biochem. 2012;359(1-2):419-29.

38. Mrabet D et al. Synovial fluid and serum levels of IL-17, IL-23, and CCL-20 in rheumatoid arthritis and psoriatic arthritis: a Tunisian cross-sectional study. Rheumatol Int. 2013;33(1):265-6.

39. Tonel G et al. Cutting edge: A critical functional role for IL-23 in psoriasis. J Immunol. 2010;185(10):5688-91.

40. Wilson NJ et al. Development, cytokine profile and function of human interleukin 17-producing helper T cells. Nat Immunol. 2007;8(9):950-7.

41. Benham H et al. Th17 and Th22 cells in psoriatic arthritis and psoriasis. Arthritis Res Ther. 2013;15(5):R136.

42. Hacquard-Bouder C et al. Alteration of antigen-independent immunologic synapse formation between dendritic cells from HLA-B27-transgenic rats and CD4+ T cells: selective impairment of costimulatory molecule engagement by mature HLA-B27. Arthritis Rheum. 2007;56(5):1478-89.

43. Costello P et al. Predominance of CD8+ T lymphocytes in psoriatic arthritis. J Rheumatol. 1999;26(5):1117-24.

44. Menon B et al. Interleukin-17+CD8+ T cells are enriched in the joints of patients with psoriatic arthritis and correlate with disease activity and joint damage progression. Arthritis Rheumatol. 2014;66(5):1272-81.

45. Lubberts E. The IL-23-IL-17 axis in inflammatory arthritis. Nat Rev Rheumatol. 2015;11(7):415-29.

46. Ory PA et al. Psoriatic arthritis and imaging. Ann Rheum Dis. 2005;64 Suppl 2:ii55-7.

47. Lubberts E et al. The role of T-cell interleukin-17 in conducting destructive arthritis: lessons from animal models. Arthritis Res Ther. 2005;7(1):29-37.

48. Chabaud M et al. IL-17 derived from juxta-articular bone and synovium contributes to joint degradation in rheumatoid arthritis. Arthritis Res. 2001;3(3):168-77.

49. Van bezooijen RL et al. Interleukin-17: A new bone acting cytokine in vitro. J Bone Miner Res. 1999;14(9):1513-21.

50. Lories RJ, McInnes IB. Primed for inflammation: enthesis-resident T cells. Nat Med. 2012;18(7):1018-9.

51. Sherlock JP et al. IL-23 induces spondyloarthropathy by acting on ROR-γt+ CD3+CD4-CD8- entheseal resident T cells. Nat Med. 2012;18(7):1069-76.

52. Nestle FO et al. Psoriasis. N Engl J Med. 2009;361(5):496-509.

53. Kopf M et al. Averting inflammation by targeting the cytokine environment. Nat Rev Drug Discov. 2010;9(9):703-18.

54. Garber K. Psoriasis: from bed to bench and back. Nat Biotechnol. 2011;29(7):563-6.

55. Mease PJ et al; Adalimumab Effectiveness in Psoriatic Arthritis Trial Study Group. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005;52(10):3279-89.

56. Mease PJ et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum. 2004;50(7):2264-72.

57. Antoni C et al; IMPACT 2 Trial Investigators. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis. 2005;64(8):1150-7.

58. Kavanaugh A et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009;60(4):976-86.

59. Mease PJ et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis. 2014;73(1):48-55.

60. Glintborg B et al. Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti-tumor necrosis factor α therapy: results from the nationwide Danish DANBIO registry. Arthritis Rheum. 2011;63(2):382-90.

61. Kavanaugh A et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis. 2014;73(6):1020-6.

62. Ritchlin C et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. 2014;73(6):990-9.

63. McInnes IB et al; PSUMMIT 1 Study Group. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013;382(9894):780-9.

64. Kavanaugh A et al; on behalf of the PSUMMIT 1 Study Group. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 2-year results from a phase 3, multicentre, double-blind, placebo-controlled study. Ann Rheum Dis. 2014;73(Suppl 2):737-8.

65. Langley RG et al; FIXTURE Study Group. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med. 2014;371(4):326-38.

66. Thaci D et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: 16-week results from the CLEAR study. American Acadamy of Dermatology 73rd Annual Meeting, 20 March 2015.

67. Mease P et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, improves active psoriatic arthritis and inhibits radiographic progression: efficacy and safety data from a phase 3 randomised, multicenter, double-blind, placebo-controlled study. Arthritis Rheum. 2014;66:S423-4.

68. McInnes IB et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, improves active psoriatic arthritis: 24-week efficacy and safety data from a phase 3 randomised, multicenter, double-blind, placebo-controlled study using subcutaneous dosing. ACR/ARHP Annual Meeting, 18 November 2014.

69. Mease P et al. Secukinumab safety and tolerability in patients with active psoriatic arthritis: pooled safety analysis of two phase 3, randomised, controlled trials (Future 1 and Future 2). Ann Rheum Dis. 2015;74:870-1.

70. Kane D et al. A classification study of clinical subsets in an inception cohort of early psoriatic peripheral arthritis--'DIP or not DIP revisited'. Rheumatology

(Oxford). 2003;42(12):1469-76.

71. Torre Alonso JC et al. Psoriatic arthritis (PA): a clinical, immunological and radiological study of 180 patients. Br J Rheumatol. 1991;30(4):245-50.

72. Siannis F et al. Clinical and radiological damage in psoriatic arthritis. Ann Rheum Dis. 2006;65(4):478-81.

73. van der Heijde D et al. Psoriatic arthritis imaging: a review of scoring methods. Ann Rheum Dis. 2005;64 Suppl 2:ii61-4.

74. van der Heijde D et al. Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: Results from the induction and maintenance psoriatic arthritis clinical trial 2. Arthritis Rheum. 2007;56(8):2698-707.

75. Goulabchand R et al. Effect of tumour necrosis factor blockers on radiographic progression of psoriatic arthritis: a systematic review and meta-analysis of randomised controlled trials. Ann Rheum Dis. 2014;73(2):414-9.

76. Kavanaugh A et al. Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials. Ann Rheum Dis. 2014;73(6):1000-6.

77. van der Heijde D et al. Secukinumab, a Monoclonal Antibody to Interleukin-17A, Provides Significant and Sustained Inhibition of Joint Structural Damage in Active Psoriatic Arthritis Regardless of Prior TNF Inhibitors or Concomitant Methotrexate: A Phase 3 Randomized, Double-Blind, Placebo Controlled Study. Abstract 954. Arthritis Rheum. 2014;66:S424.

78. Smolen JS et al. New therapies for treatment of rheumatoid arthritis. Lancet. 2007;370(9602):1861-74.

79. Gossec L et al; European League Against Rheumatism. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. Ann Rheum Dis. 2012;71(1):4-12.

80. Gladman DD et al. Do patients with psoriatic arthritis who present early fare better than those presenting later in the disease? Ann Rheum Dis. 2011;70(12): 2152-4.

81. Smolen JS et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. Ann Rheum Dis. 2014;73(1):6-16.

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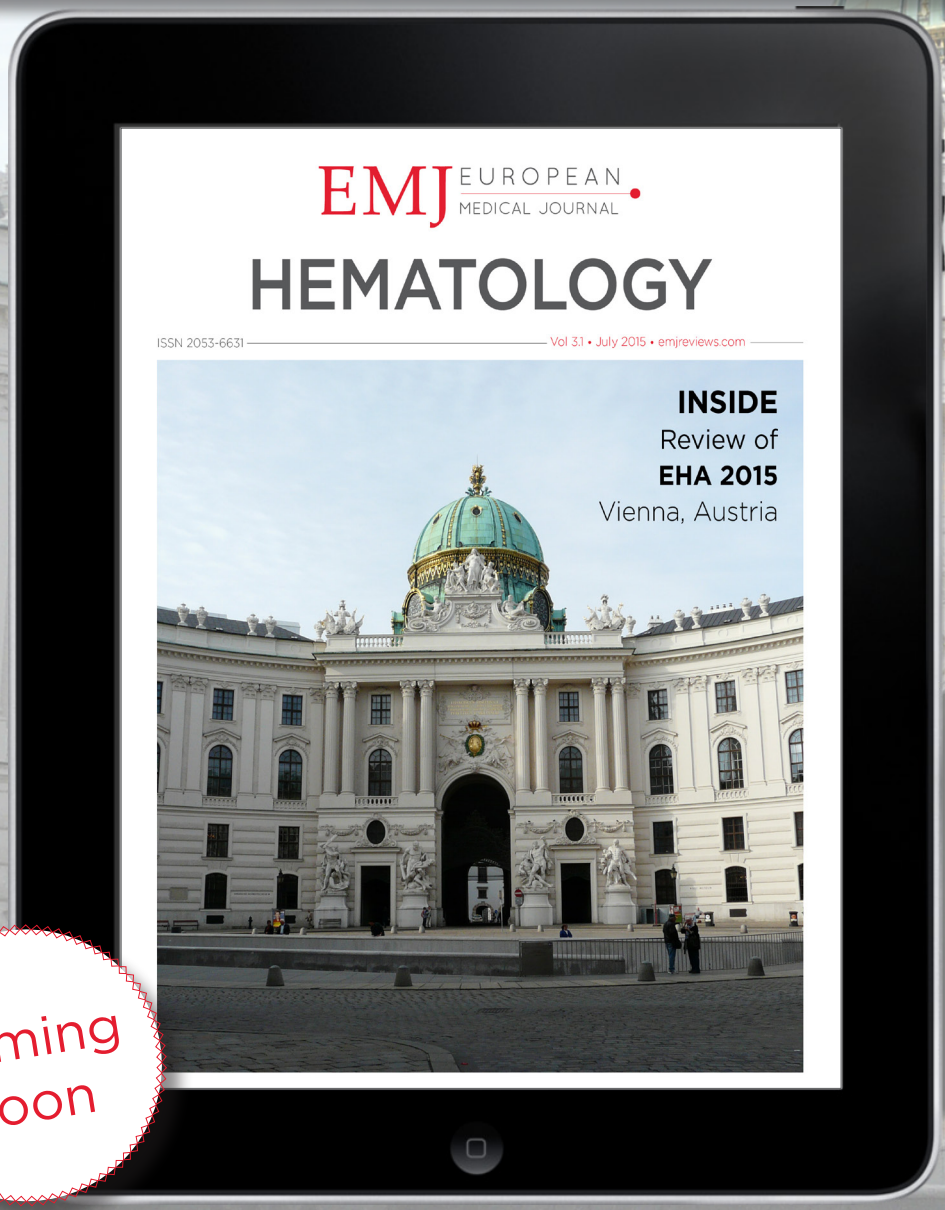

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PREGNANCY IN CHRONIC ARTHRITIS: ONLY A MATTER OF PLANNING

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ABSTRACT

Chronic arthritis often affects women of childbearing age. The old concept that having chronic arthritis constitutes a major obstacle to women when planning a pregnancy is now obsolete. Thanks to our current capacity to control the activity of rheumatoid arthritis and other chronic inflammatory conditions, and due to the availability of highly effective drugs such as tumour necrosis factor inhibitor agents and other biological agents, many women with these diseases are now able to consider the challenge of childbearing and raising children. Careful pre-conceptional evaluation and risk assessment constitutes the first step of proper care, which can be individualised according to the disease. More than ever, rheumatologists must know how to deal with this situation, and must be able to provide adequate counselling regarding the control of arthritis during conception and pregnancy.

Keywords: Counselling, pregnancy outcome, rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis (PsA), teratogenicity, biological therapies, disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids (GCs), non-steroidal anti-inflammatory drugs (NSAIDs).

INTRODUCTION

The old concept that having chronic arthritis constitutes a major obstacle to women when planning a pregnancy is now obsolete. Thanks to our current capacity to control the activity of rheumatoid arthritis (RA) and other chronic inflammatory conditions, and due to the availability of highly effective drugs such as tumour necrosis factor inhibitor (anti-TNF) agents and other biological agents, many women with these diseases are now able to consider the challenge of childbearing and raising children. Careful pre-conceptional evaluation and risk assessment is important. More than ever, rheumatologists must know how to deal with this situation and must be able to provide adequate counselling regarding the control of arthritis during conception and pregnancy.

Prevention of unplanned pregnancy is an essential step to success: all medication must be reviewed before pregnancy in order to prevent risks to the unborn child due to drug exposure. Maintaining remission or low disease activity before and during pregnancy is crucial for good outcomes: active disease at conception usually continues to be active throughout pregnancy and increases the risk of a post-partum flare.[1] In RA patients, it is important to carry out an assessment of certain antibodies that may require special monitoring, such as anti-Ro, anti-La, and antiphospholipid antibodies.[2,3]

The Effect of Pregnancy on Arthritis

Although a traditional belief considers that RA improves during pregnancy, recent literature has shown that this is not so. A study of approximately 90 pregnancies reported by de Man et al.[4] observed that at least 50% of patients with moderate-to-high disease activity during the first trimester had no clinical improvement as defined by the European League Against Rheumatism

criteria,[5] and almost 50% overall had at least moderate disease activity during the third trimester. The same author noticed a higher probability of improvement during pregnancy in seronegative women (negative for rheumatoid factor and anticitrullinated peptide antibodies).[6] Patients with low disease activity usually remain stable throughout pregnancy, whereas those with high disease activity at conception have less chance of improvement during pregnancy.[7]

Not all forms of chronic arthritis behave similarly during pregnancy: only one-third of women with ankylosing spondylitis show improvement, while another one-third remain stable and the rest worsen. After delivery, 60% of the women will suffer an outbreak.[8] Women with psoriatic arthritis (PsA) improve or experience disease remission in 80% of pregnancies, although approximately 70% experience a post-partum flare during the first 3 months after delivery.[9]

The Effect of Active Arthritis on Pregnancy

It is likely that most rheumatologists tend to interrupt drug therapies when a pregnancy is planned because of concerns about possible detrimental effects on the fetus. However, growing evidence about the inconvenience of an active disease during pregnancy, with serious materno-fetal consequences, is forcing us to reconsider this position. An association between high disease activity during pregnancy and poor pregnancy outcomes has been demonstrated in several studies,[10-12] with greater incidence of pre-term delivery and lower birth-weight infants resulting in an increased risk of perinatal mortality.[13] Moreover, caesarean sections were performed significantly more often in a group with intermediate or high disease activity compared with a group with low disease activity (22% versus 10%, p=0.04 by chi-squared test).[10] Recently, a relationship between elevated RA disease activity during pregnancy and rapid post-natal catch-up in weight of the offspring has been found, with the latter associated with a worse cardiovascular and metabolic profile in early adulthood.[14] Finding the balance between the side-effects of disease-modifying anti-rheumatic drugs (DMARDs) and the control of disease is a challenge; each case must be managed on an individual basis to provide the least possible risk to the mother and to the fetus and neonate, but at the same time minimising adverse events due to disease.

The Effect of Drugs on Mother and Child

For the mother, a drug can be considered safe during pregnancy if it produces no additional side-effects than when used in non-pregnant patients, if it does not increase the rate of complications such as miscarriage or prematurity, and may be considered safe in the child if it does not produce short or long-term adverse effects. A teratogen is an agent that has the potential to interfere with the normal functional or structural development of an embryo or fetus. During organogenesis (15-60 days after conception), the fetus is presumed to be most vulnerable to teratogens. Gross anatomical defects are no longer possible once the definitive form and relationships within an organ system are established, although derangements in the function of organ systems and resulting physiological defects and fetal growth restriction may be present later in pregnancy.[15] The USA FDA has established five categories that classify the safety of drugs when used during pregnancy (Table 1).[16] However, new requirements published in December 2014 (effective from 30th June, 2015) substitute for these categories by providing a summary of the risks of using a drug during pregnancy and lactation, a discussion of the data supporting that summary, and relevant information to help healthcare providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation.[17]

In patients planning a pregnancy, adjustment of therapy is mandatory. Patients must understand the importance of low disease activity before conception and throughout pregnancy, and therefore the need to maintain the use of certain drugs. On the basis of consensus opinion: corticosteroids and analgesics such as paracetamol can be used throughout pregnancy; non-steroidal anti-inflammatory drugs (NSAIDs) must be avoided during the conception cycle and used sparingly in the first trimester, but can be administered safely until Week 30 of gestation; anti-malarials, sulfasalazine, azathioprine, and cyclosporine are compatible with pregnancy; and methotrexate (MTX), leflunomide (LEF), and biological agents should be withdrawn before a planned pregnancy.[18] The most recent information regarding certain biological agents, such as anti-TNF agents, suggests that these medications can be continued in certain circumstances.[19] Unfortunately, the number of controlled studies of drugs performed in pregnant women is small

and experience with therapy often derives from conditions other than rheumatic diseases.[20]

SAFETY OF DRUG CLASSES MOST COMMONLY USED IN CHRONIC ARTHRITIS PATIENTS DURING PREGNANCY

Non-Steroidal Anti-Inflammatory Drugs

The FDA considers these agents Category B (Table 2). Aspirin can be used throughout pregnancy. Other NSAIDs should be discontinued at the beginning of a conception cycle in order to increase the likelihood of ovulation and, if fertilisation occurs, subsequent implantation.[21] These drugs can then be continued up to Week 30 of gestation since there are no data for teratogenic effects, but they should then be stopped because of the risk of premature closure of the ductus arteriosus.[22] Constriction of the ductus can be seen in approximately 10-50% of fetuses after Week 31. This effect can be avoided if the NSAID is withdrawn 8 weeks before delivery.[23] There are limited data on the use of COX-2 inhibitors during pregnancy. Constriction of the ductus appears to be less pronounced but a recent study suggests that they may increase the risk of congenital anomalies.[24] Therefore, COX-2 inhibitors are considered Category C and should be avoided during pregnancy (Table 2).

Table 1: FDA risk-classification system for drug safety during pregnancy.[16]

Category A: safety established Controlled studies in women fail to demonstrate a risk to the fetus during the first trimester, there is no evidence of risk during later trimesters, and the possibility of fetal harm appears remote.
Category B: safety likely Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed by controlled studies in women during the first trimester and there is no evidence of a risk during later trimesters.
Category C: teratogenicity possible Either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) and there are no controlled studies in women, or studies in women and animals are not available. These drugs should be given only if the potential benefit justifies the potential risk to the fetus.
Category D: teratogenicity probable There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Category X: teratogenicity likely – contraindicated in pregnancy Studies in animals and humans have demonstrated fetal abnormalities and/or there is evidence of fetal risk based on human experience and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. These drugs are contraindicated in women who are, or may become, pregnant.

Table 2: Toxicities of drugs most commonly used in chronic arthritis patients during pregnancy.

Drug	USA FDA risk category[16]	Toxicity concerns:	
		Maternal	Fetal
Non-fluorinated glucocorticoids (prednisone, prednisolone)	B	Pre-term premature rupture of membranes, hypertension, gestational diabetes	Small for gestational age, adrenal hypoplasia, increased risk of cleft lip or palate
Sulfasalazine	B	None	None
Anakinra	B	None	Inadequate data
Anti-TNF agents	B	None	None
Aspirin and NSAIDs	B	Reduced fertility when used during a conception cycle	Premature closure of the ductus arteriosus when used after Week 30

Table 2 continued.

Drug	USA FDA risk category[16]	Toxicity concerns:	
		Maternal	Fetal
COX-2 selective inhibitors	C		Possible increase in malformation risk
Hydroxychloroquine	C	None	None
Cyclosporine A	C	None	Small for gestational age, prematurity, intrauterine growth retardation, transient hyperkalaemia in neonates
Rituximab	C	None	Reports of haematological abnormalities, infection
Abatacept	C	None	Inadequate data
Tocilizumab	C	None	Inadequate data
Tofacitinib	C	None	Inadequate data
Azathioprine	D	None	Small for gestational age, prematurity, intrauterine growth retardation
Methotrexate	X	None	Abortogenic, craniofacial anomalies, mental retardation
Leflunomide	X	None	Craniofacial anomalies

Anti-TNF agents: tumour necrosis factor inhibitor agents; NSAID: non-steroidal anti-inflammatory drug.

Glucocorticoids

Glucocorticoids (GCs) are frequently used in the management of pregnant patients with chronic arthritis and are considered Category B (Table 2). When active arthritis affects only one or a limited number of joints, intra-articular steroid injections can be very useful. Recently, prednisone use during pregnancy in RA patients has been associated with unfavourable outcomes as described by a study of 31 RA pregnancies followed prospectively in a single clinic. The patients with neither prednisone nor anti-TNF exposure had a mean first trimester disease activity score — C-reactive protein (DAS-CRP) of 1.63, while patients exposed to prednisone or anti-TNF had a mean DAS-CRP of 3.92 or 3.19, respectively. An adverse outcome (pre-term birth and/or pre-eclampsia) occurred in 54.2% of patients exposed to prednisone compared with 14.3% of those with anti-TNF exposure, suggesting that the latter may be preferable to prednisone in pregnant women with active RA.[25] There are reports suggesting that GC exposure during the first trimester may increase the risk of cleft lip or palate, but no other major congenital anomalies; women should be counselled about this potential risk. Other adverse effects associated with prednisone use during pregnancy are pre-term premature rupture of membranes and children who are relatively small for their gestational age.

Disease-Modifying Anti-Rheumatic Drugs

Both MTX and LEF are considered as Category X (Table 2). MTX is teratogenic and embryotoxic, and its use during pregnancy is associated with multiple abnormalities, most often involving the central nervous system, cranial ossification, and the palate (aminopterin syndrome).[26] The drug is contraindicated during pregnancy and should be prescribed to fertile women only under the condition of safe contraception. It has been proposed that conception should be postponed until 3 months after withdrawal of the drug,[27] although this may be too conservative. Since MTX is a folic acid antagonist, folate supplementation should be continued antenatally and throughout pregnancy. There are no definitive data on whether the offspring of men receiving MTX have an increased risk of teratogenicity, although it is usually recommended that men discontinue this medication for 1-3 months prior to attempting conception.[28]

LEF is a pyrimidine synthesis inhibitor that is both embryotoxic and teratogenic in animals. Women of childbearing potential for whom LEF is prescribed must be advised to avoid pregnancy. In a follow-up study of 45 women exposed to LEF prior to or during pregnancy, there was a 12.5% incidence of congenital anomalies in the 16 patients exposed during the first trimester, which is higher than the generally reported background rate of 3%.[29] Due to its long half-life and protracted elimination from plasma, LEF-treated patients must follow a cholestyramine drug elimination procedure ('wash out') and then wait at least 90 days before attempting pregnancy: cholestyramine 8 g is given three-times daily for 11 days and plasma levels, checked twice 2 weeks apart, should be below 0.02 mg/l, with additional cholestyramine administration if the level is higher than this cut-off value.[30] For those who inadvertently become pregnant while taking LEF, this 'wash out' procedure early during pregnancy can allow the continuation of the pregnancy, with an absence of substantially increased risk of adverse pregnancy outcomes, as has been previously demonstrated.[31]

Sulfasalazine is considered to be Category B (Table 2). Although both the molecule and its metabolite, sulfapyridine, do cross the placenta, they do not have a significant clinical impact on the fetus. The main data describing pregnancies exposed to sulfasalazine were derived from the treatment of patients with inflammatory bowel disease (IBD), and no increases in birth defects, pathological jaundice, or babies who were small for their gestational age were detected.[32-34] Because the drug is a strong inhibitor of the reduced folate carrier, folate supplementation before and throughout pregnancy must be ensured.[35] Maternal doses should not exceed 2 g daily in order to avoid the risk of neutropaenia in the newborn.[36] Sulfasalazine impedes spermatogenesis, causing azoospermia, and so men should discontinue this medication 3 months prior to attempting conception.[37]

Cyclosporine is also a treatment option, especially for RA and PsA patients, and is considered Category C (Table 2). More than 800 pregnancies exposed to cyclosporine for several weeks or throughout gestation have been reported, with the majority being in transplant recipients,[28,38] and there was no incremental increase in congenital malformations. Renal and liver functions were both normal in the neonates exposed.[39] The major problems associated with pregnancies exposed to cyclosporine treatment were prematurity in 40-46% and low birth weight (<2,500 g) in 44-65% of cases, but it has been difficult to ascribe a causative role to drug treatment or the underlying maternal disorder.

Azathioprine is not metabolised to its active form by the placenta and so hardly reaches the developing fetus. Pregnancy data from large transplant registries,[40,41] as well as women with systemic lupus erythematosus[42,43] and IBD,[44] found no predominant or frequent birth defect. Although the drug is considered Category D (Table 2) for use during pregnancy, there is substantial evidence suggesting that it is not teratogenic. Intrauterine exposure to azathioprine may occasionally cause slight suppression of the bone marrow, as shown by decreased leukocyte counts and thrombocytopaenia at birth.[45] Doses should be maintained at 1.5-2 mg/kg/day in order to avoid neonatal depression of haematopoiesis. There are conflicting reports in the literature as to whether these medications increase the risk of children being small for their gestational age. Hydroxychloroquine is classified as Category C (Table 2), but does not appear to cause fetal toxicity and can be used safely.[46,47]

Biological Agents

As in non-pregnant individuals, the use of biological agents increases the potential risk of infections. This is especially important for pathogens such as *Listeria monocytogenes*, for which the risk is already increased in pregnant women[48] and can be further increased by treatment.[49] Current manufacturers' guidelines recommend the stopping of all currently licensed biological therapies prior to conception, primarily due to the lack of controlled studies in pregnant women. However, there is now a huge amount of information available regarding their use during conception, pregnancy, and breastfeeding.[50] Much of this post-marketing experience has been obtained through registries, especially in the field of IBD. In many cases, not treating IBD or discontinuing therapy prior to or during pregnancy may pose a greater risk to mother and fetus,[20] while maintaining treatment appears to be of lower risk.

Tumour necrosis factor inhibitors

Anti-TNF agents, such as adalimumab (ADA), certolizumab (CZP), etanercept, golimumab,

and infliximab (IFX), are considered Category B (Table 2). Although some case reports of congenital anomalies (VACTERL anomalies) following exposure to anti-TNF agents raised concerns about their safety profile when used during pregnancy, numerous case series of pregnancies exposed to anti-TNF agents, as well as several recent systematic literature reviews, have failed to find maternal toxicity, embryotoxicity, or teratogenicity.[51,52] In the pregnant woman, maternal transfer of immunoglobulins across the syncytiotrophoblast of the chorionic villi provides fetal immunity and is mediated by the neonatal Fc receptor. Immunoglobulin G (IgG) concentrations in fetal blood increase steadily from the early stages of the second trimester until delivery.[53] Small amounts of biological agents will pass into the fetal circulation during early pregnancy, when organogenesis is underway, suggesting that women can be reassured that the use of anti-TNF agents during the peri-conceptional period, until pregnancy is established, should be low risk. By continuing anti-TNF at least until established pregnancy is confirmed, women who are hoping to conceive should not need to risk disease flare during the period between stopping teratogenic medications, such as MTX, and successful conception.

However, most of the safety data available are derived from women discontinuing anti-TNF therapy during the first trimester; few data exist regarding exposure throughout pregnancy. Due to the different composition of anti-TNF agents, some risks may depend on the individual agent rather than the drug class itself. Both IFX and ADA belong to the IgG1 subclass of antibodies and are capable of crossing the placental barrier, particularly during the second half of pregnancy. At birth, both infant and cord blood demonstrated higher concentrations of IFX and ADA. This raises concerns about infections, safety of vaccination, and, in general, about the development of the immune system of the child: serious infections in infants exposed to anti-TNF agents have been described,[54] and a case of fatal disseminated tuberculosis after Bacillus Calmette–Guérin (BCG) vaccination of a child exposed to IFX *intra-utero* has been described.[55] In contrast, very low concentrations of CZP were observed in infant and cord blood when mothers were treated with CZP.[56] This is attributed to the absence of an Fc domain on the CZP molecule, which prevents it being bound by the neonatal Fc receptor.[57] Therefore, it is recommended that live vaccines (including rotavirus, intranasal influenza vaccine, and BCG) be withheld for 6 months from birth in neonates who have had *in utero* exposure to anti-TNF agents, except CZP due to its minimal transfer. Other vaccines can be given on schedule.

Recent data from the multinational PIANO registry provide reassurance regarding the potential long-term effects on children exposed *in utero* to anti-TNF agents. A total of 501 women with IBD were followed through pregnancy and during the first 4 years of the child's life and exposure to biological therapy during the third trimester of pregnancy was not associated with increased infant infection rates,[58] and children did not exhibit developmental delay compared with infants not exposed to these agents, controlling for pre-term birth.[59]

Other biological agents

Anakinra is a recombinant interleukin (IL)-1 receptor antagonist. In animal studies, no harm to the fetus has been demonstrated. The drug is considered Category B but little has been reported about its safety in this setting (Table 2). Tocilizumab is a monoclonal antibody directed against IL-6 receptors and capable of blocking downstream signalling. The drug is considered Category C and no teratogenicity has been demonstrated in animal models, although at high dose there was increased risk of abortion (Table 2). Abatacept works by blocking interactions between antigen-presenting cells and T cells via binding to CD80/CD86 on antigen-presenting cells, with subsequent inhibition of T cell activation. The drug is considered Category C and there are inadequate data to fully comment on its safety during pregnancy (Table 2), although animal studies saw no increased risk when exposed to the maximum recommended human dose. Current recommendations are to discontinue therapy at least 10 weeks before conception. Rituximab, a monoclonal antibody directed against CD20, depletes B cells. Animal studies are limited but show no teratogenic effect, although B cells have been demonstrated to be reduced in offspring.[60]

The drug is considered Category C (Table 2) and there are limited data available; it is recommended that, ideally, at least 12 months should elapse between rituximab discontinuation and conception.

Table 3: Practical points to consider when treating women of childbearing age with chronic arthritis.

Before pregnancy	• Talk to the patient and her partner about risks • Schedule pregnancy: - Find a time of remission or low disease activity - Stop teratogenic drugs (methotrexate, leflunomide) and replace them with safer alternatives (sulfasalazine, hydroxychloroquine) • Agree on treatment strategy with the patient and her partner: - Maintain or do not maintain the biological drug - Decide which attitude to adopt during pregnancy if the disease becomes active • Individualise treatment: - Risk of disease activation - Risk of maintaining biological treatment
Some practical clues	• Patients with inactive disease and receiving non-biological and/or non-teratogenic drugs: consider drug holiday • Patients with inactive disease and receiving teratogenic drugs: stop current drugs and replace with safer alternative(s) • Patients with active disease requiring teratogenic drugs (methotrexate, leflunomide): transition to anti-TNF therapy • Patients with inactive disease on anti-TNF therapy: maintain therapy up to confirmed pregnancy test, consider therapy through to Week 32 of gestation • Disease becomes active during pregnancy: consider maintaining anti-TNF throughout pregnancy (try to use those with less placental transfer)

TNF: tumour necrosis factor.

Tofacitinib is a Janus kinase inhibitor recently approved by FDA for RA, although not approved in Europe. The drug is classified as Category C (Table 2) and there are no available data describing its safety during pregnancy. Ustekinumab is considered Category B, with data in humans being limited to case reports. A recent abstract described 26 completed pregnancies that involved ustekinumab exposure in the course of treatment of psoriasis, and which documented a rate of spontaneous abortions comparable to that observed in the general population.[61]

CONCLUSION

Chronic arthritis often affects women of childbearing age. Counselling of the pre-pregnancy patient constitutes the first step of proper care. Complete information regarding risks must be offered to the patient and her partner, and should be individualised according to the disease (Table 3). At the time of conception, the disease must be under control with medications compatible with pregnancy in order to minimise the risks. Ideally, drug treatment during pregnancy should control the mother's disease activity, do no harm to the fetus, and ensure a healthy period of pregnancy for mother and child. An interdisciplinary approach between the rheumatologist, obstetrician, and eventually the paediatrician, is needed in order to ensure success. Currently, we can say that pregnancy in chronic arthritis patients is only a matter of planning.

REFERENCES

1. Förger F et al. Pregnancy mediated improvement of rheumatoid arthritis. Swiss Med Wkly. 2012;142:w13644.

2. Cavazzana I et al. Anti-Ro/SSA antibodies in rheumatoid arthritis: clinical and immunologic associations. Clin Exp Rheumatol. 2006;24:59-64.

3. Olech E, Merrill JT. The prevalence and clinical significance of antiphospholipid antibodies in rheumatoid arthritis. Curr Rheumatol Rep. 2006;8:100-8.

4. de Man YA et al. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. Arthritis Rheum. 2008;59:1241-8.

5. van Gestel AM et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum. 1996;39:34-40.

6. de Man YA et al. Women with rheumatoid arthritis negative for anticyclic citrullinated peptide and rheumatoid factor are more likely to improve during pregnancy, whereas in autoantibody-positive women autoantibody levels are not influenced by pregnancy. Ann Rheum Dis. 2010;69:420-3.

7. de Man YA et al. Disease activity of

rheumatoid arthritis during pregnancy: results from a nationwide prospective study. Arthritis Rheum. 2008;59:1241-8.

8. Ostensen M, Ostensen H. Ankylosing spondylitis--the female aspect. J Rheumatol. 1998;25:120-4.

9. Ostensen M. The effect of pregnancy on ankylosing spondylitis, psoriatic arthritis, and juvenile rheumatoid arthritis. Am J Reprod Immunol. 1992;28:235-7.

10. de Man YA et al. Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight results of a national prospective study. Arthritis Rheum. 2009;60:3196-206.

11. Chakravarty EF. Rheumatoid arthritis and pregnancy: beyond smaller and preterm babies. Arthritis Rheum. 2011;63:1469-71.

12. Langen ES et al. High rate of preterm birth in pregnancies complicated by rheumatoid arthritis. Am J Perinatol. 2014;31:9-14.

13. Wallenius M et al. Pregnancy and delivery in women with chronic inflammatory arthritides with a specific focus on first birth. Arthritis Rheum. 2011;63:1534-42.

14. de Steenwinkel FD et al. Rheumatoid arthritis during pregnancy and postnatal catch-up growth in the offspring. Arthritis Rheumatol. 2014;66:1705-11.

15. Blackburn ST, "Pharmacology and Pharmacokinetics during the Perinatal Period," Blackburn ST (ed.), Maternal, Fetal, & Neonatal Physiology: a Clinical Perspective (2013) 4th edition, Maryland Heights: Saunders, pp. 183-202.

16. U.S. Food and Drug Administration. CFR - Code of Federal Regulations Title 21. 2014. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=201.57. Last accessed: 29 May 2015.

17. U.S. Food and Drug Administration. Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. April 2014. Available at: https://www.federalregister.gov/articles/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for#page-72063. Last accessed: 29 May 2015.

18. Østensen M, Förger F. Management of RA medications in pregnant patients. Nat Rev Rheumatol. 2009;5:382-90.

19. Hyrich KL, Verstappen SM. Biologic therapies and pregnancy: the story so far. Rheumatology (Oxford). 2014;53:1377-85.

20. Hassid B, Mahadevan U. The use of biologic therapy in pregnancy: a gastroenterologist's perspective. Curr Opin Rheumatol. 2014;26:347-53.

21. Pall M et al. Induction of delayed follicular rupture in the human by the selective COX-2 inhibitor rofecoxib: a randomized double-blind study. Hum Reprod. 2001;16:1323-8.

22. Alano MA et al. Analysis of nonsteroidal antiinflammatory drugs in meconium and its relation to persistent pulmonary hypertension of the newborn. Pediatrics. 2001;107:519-23.

23. Ostensen M, Ostensen H. Safety of nonsteroidal antiinflammatory drugs in pregnant patients with rheumatic disease. J Rheumatol. 1996;23:1045-9.

24. Daniel S et al. Major malformations following exposure to nonsteroidal antiinflammatory drugs during the first trimester of pregnancy. J Rheumatol. 2012;39:2163-9.

25. Chaudhary P, Clowse MEB. Prednisone use associated with worse outcomes in rheumatoid arthritis pregnancies. Arthritis Rheum. 2013;65 Suppl 10:1330.

26. Lloyd ME et al. The effects of methotrexate on pregnancy, fertility and lactation. QJM. 1999;92:551-63.

27. Donnenfeld AE et al. Methotrexate exposure prior to and during pregnancy. Teratology. 1994;49:79-81.

28. Bar Oz B et al. Pregnancy outcome after cyclosporine therapy during pregnancy: a meta-analysis. Transplantation. 2001;71:1051-5.

29. Cassina M et al. Pregnancy outcome in women exposed to leflunomide before or during pregnancy. Arthritis Rheum. 2012;64:2085-94.

30. Brent RL. Teratogen update: reproductive risks of leflunomide (Arava); a pyrimidine synthesis inhibitor: counseling women taking leflunomide before or during pregnancy and men taking leflunomide who are contemplating fathering a child. Teratology. 2001;63:106-12.

31. Chambers CD et al. Birth outcomes in women who have taken leflunomide during pregnancy. Arthritis Rheum. 2010;62:1494-503.

32. Nørgård B et al. Population-based case control study of the safety of sulfasalazine use during pregnancy. Aliment Pharmacol Ther. 2001;15:483-6.

33. Mogadam M et al. Pregnancy in inflammatory bowel disease: effect of sulphasalazine and corticosteroids on fetal outcome. Gastroenterology. 1981;80:72-6.

34. Rahimi R et al. Pregnancy outcome in women with inflammatory bowel disease following exposure to 5-aminosalicylic acid drugs: a meta-analysis. Reprod Toxicol. 2008;25:271-5.

35. Hernández-Díaz S et al. Folic acid antagonists during pregnancy and the risk of birth defects. N Engl J Med. 2000;343:1608-14.

36. Levi S et al. Reversible congenital neutropenia associated with maternal sulphasalazine therapy (letter). Eur J Pediat. 1988;148:174-5.

37. Chatzinoff M et al. Sulfasalazine-induced abnormal sperm penetration assay reversed on changing to 5-aminosalicylic acid enemas. Dig Dis Sci. 1988;33:108-10.

38. Lamarque V et al. Analysis of 629 pregnancy outcomes in transplant recipients treated with Sandimmun. Transplant Proc. 1997;29:2480.

39. Shaheen FAM et al. Long-term nephrotoxicity after exposure to cyclosporine in utero. Transplantation. 1993;56:224-25.

40. Registration Committee of the European Dialysis and Transplant Association. Successful pregnancies in women treated by dialysis and kidney transplantation. Report from the Registration Committee of the European Dialysis and Transplant Association. Br J Obstet Gynaecol. 1980;87:839-85.

41. Radomski JS et al. Outcomes of 500 pregnancies in 335 female kidney, liver, and heart transplant recipients. Transplant Proc. 1995;27:1089-90.

42. Meehan RT, Dorsey JK. Pregnancy among patients with systemic lupus erythematosus receiving immunosuppressive therapy. J Rheumatol. 1987;14:252-8.

43. Ramsey-Goldman R et al. Pregnancy outcome in women with systemic lupus erythematosus treated with immunosuppressive drugs. J Rheumatol. 1993;20:1152-7.

44. Casanova MJ et al. Safety of thiopurines and anti-TNF-α drugs during pregnancy in patients with inflammatory bowel disease. Am J Gastroenterol. 2013;108:433-40.

45. Davison JM et al. Maternal azathioprine therapy and depressed haemopoiesis in the babies of renal allograft patients. Br J Obst Gynecol. 1985;92:233-9.

46. Sperber K et al. Systematic review of hydroxychloroquine use in pregnant patients with autoimmune diseases. Pediatr Rheumatol Online J. 2009;7:9.

47. Bermas BL. Non-steroidal anti inflammatory drugs, glucocorticoids and disease modifying anti-rheumatic drugs for the management of rheumatoid arthritis before and during pregnancy. Curr Opin Rheumatol. 2014;26:334-40.

48. Southwick FS, Purich DL. Intracellular pathogenesis of listeriosis. N Engl J Med. 1996;21;334:770-6.

49. Peña-Sagredo JL et al. Listeria monocytogenes infection in patients with rheumatic diseases on TNF-alpha antagonist therapy: the Spanish Study Group experience. Clin Exp Rheumatol.

2008;26:854-9.

50. Vinet E et al. Biologic therapy and pregnancy outcomes in women with rheumatic diseases. Arthritis Rheum. 2009;61:587-92.

51. Nielsen O et al. Safety of TNF-α inhibitors during IBD pregnancy: a systematic review. BMC Med. 2013;11:174.

52. Marchioni RM, Lichtenstein GR. Tumor necrosis factor-α inhibitor therapy and fetal risk: a systematic literature review. World J Gastroenterol. 2013;19:2591-602.

53. Palmeira P et al. IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol. 2012;2012:985646.

54. Johnsson A et al. Chicken pox infection in a three months old infant exposed in utero to Adalimumab. J Crohns Colitis. 2013;7:e116-7.

55. Cheent K et al. Case Report: Fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. J Crohns Colitis. 2010;4:603-5.

56. Mahadevan U et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2013;11:286-92.

57. Clowse MEB et al. Retrospective analysis of certolizumab pegol use during pregnancy: update of impact on birth outcomes. Arthritis Rheum. 2013;65 Suppl 10:433.

58. Mahadevan U et al. Exposure to anti-TNFα therapy in the third trimester of pregnancy is not associated with increased adverse outcomes: results from the PIANO Registry. Gastroenterol. 2014:146 suppl 1:S-170.

59. Mahadevan U et al. Achievement of developmental milestones among offspring of women with inflammatory bowel disease: the PIANO Registry. Gastroenterol. 2014:146 suppl 1:S-1.

60. Chakravarty EF et al. Pregnancy outcomes after maternal exposure to rituximab. Blood. 2011;117:1499-506.

61. Cather JC et al. Pregnancy outcomes in women exposed to ustekinumab in the psoriasis clinical development program. Australasian Journal of Dermatology. 2014;55 suppl 1:1-58.

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OBESITY AND OSTEOARTHRITIS: MORE THAN JUST MECHANICS

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ABSTRACT

Osteoarthritis (OA) is the most common form of arthritis worldwide. It results in chronic pain, functional limitations, and significant social and economic burdens. Obesity rates in the developed world are rapidly increasing, leading to warnings of an obesity epidemic. Obesity is associated with increased rates of OA. Traditionally, this increased prevalence was attributed to biomechanical factors including increased joint loading and altered joint dynamics due to the physical burden of obesity. However, a number of factors, including the increased prevalence of OA in non-weight-bearing joints in obese individuals and the increasing awareness of adipose tissue as a functional endocrine organ rather than an inert storage substance, have led to a reappraisal of this viewpoint. Adipose tissue secretes a number of adipokines and cytokines with both local and systemic effects. In addition, adipose tissue has the potential to stimulate a systemic inflammatory state. Differential expression of microRNAs in obese and non-obese osteoarthritic patients has been demonstrated. The potential impact of adipokines on the adipose inflammatory pathway in obese individuals is being actively explored. The traditional view of OA as a mechanical wear-and-tear disease is being revolutionised by the discovery of the key roles of inflammation and cytokines in this most common of joint diseases.

Keywords: Obesity, osteoarthritis, adipokines, inflammation, cytokines, microRNA.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis worldwide.[1] There is a significant discrepancy between radiographic changes and patient-reported symptoms in OA. Many patients report no symptoms but have significant radiographic changes of OA.[2] Symptomatic OA presents with predominant symptoms of pain and stiffness. This can lead to significant disability and difficulty performing activities of daily living.[1,3,4] Severely symptomatic OA frequently necessitates joint replacement surgery, with high attendant costs involved.[5]

The global prevalences of symptomatic and radiographic OA at the knee and hip are 3.8% and 0.85%, respectively.[1] Radiographic hand OA is present in 67% of women and 55% of men aged 55 years and over, with one-fifth of these experiencing symptoms.[2,6] In addition, OA at other sites contributes significantly to the high prevalence of many other musculoskeletal complaints such as low back pain, which is the leading cause of 'years lived with disability' worldwide.[4] OA is strongly associated with ageing and therefore we can expect to see a further increase in prevalence due to the ongoing demographic changes in our population.[7] The traditional view of OA maintained that it was a 'wear-and-tear' form of arthritis caused by repetitive activity over many years and was an inevitable consequence of ageing.[8] Factors resulting in increased joint loading, such as excessive physical activity or body weight, were accepted as risk factors.[9] A deeper understanding of the pathogenesis of OA has led to the recognition of genetic factors, biomechanical factors, and inflammatory processes as important elements in the development of OA.[10-12]

Obesity is rapidly becoming one of the world's most significant health issues, with 2.1 billion people either overweight or obese in 2013.[13] Obesity has long been recognised as a risk factor for OA.[9] This was initially attributed to increased force through weight-bearing joints. However, this was challenged by the association of obesity with OA of non-weight-bearing joints, such as the hands.[14,15] Body composition in terms of both reduced skeletal muscle mass and increased fat mass may be more predictive of OA and cartilage loss than body mass index (BMI).[16,17] Adiposity measures are strongly associated with the need for joint replacement surgery.[18] Adipose tissue was previously regarded as an inert storage vessel but new insights have revealed that it is in fact an endocrine organ actively secreting a variety of adipokines and cytokines with a multitude of local and systemic effects.[19] The purpose of this review is to explore the role of obesity in the development of OA from a metabolic viewpoint (Figure 1).

ADIPOKINES

Adipokines are proteins secreted by adipocytes. There are over 100 adipokines identified to date, the most studied of which include leptin, adiponectin, resistin, visfatin, chemerin, and lipocalin 2.[20] In addition to these adipokines, adipose tissue also contains a population of resident macrophages that secrete a variety of cytokines, including tumour necrosis factor alpha (TNFα) and interleukin (IL)-6.[19]

Leptin

Leptin is a 16-kDa protein encoded by the *OB* gene, and which circulates in human plasma.[21] Since its discovery 20 years ago it has been considered as the prototype for other adipokines.[20] The key physiological roles of leptins are in satiety and appetite.[20] Leptin levels are associated with fat mass, BMI, and circulating levels of inflammatory markers.[22] Serum leptin levels correlate with the severity of radiographic knee OA.[23]

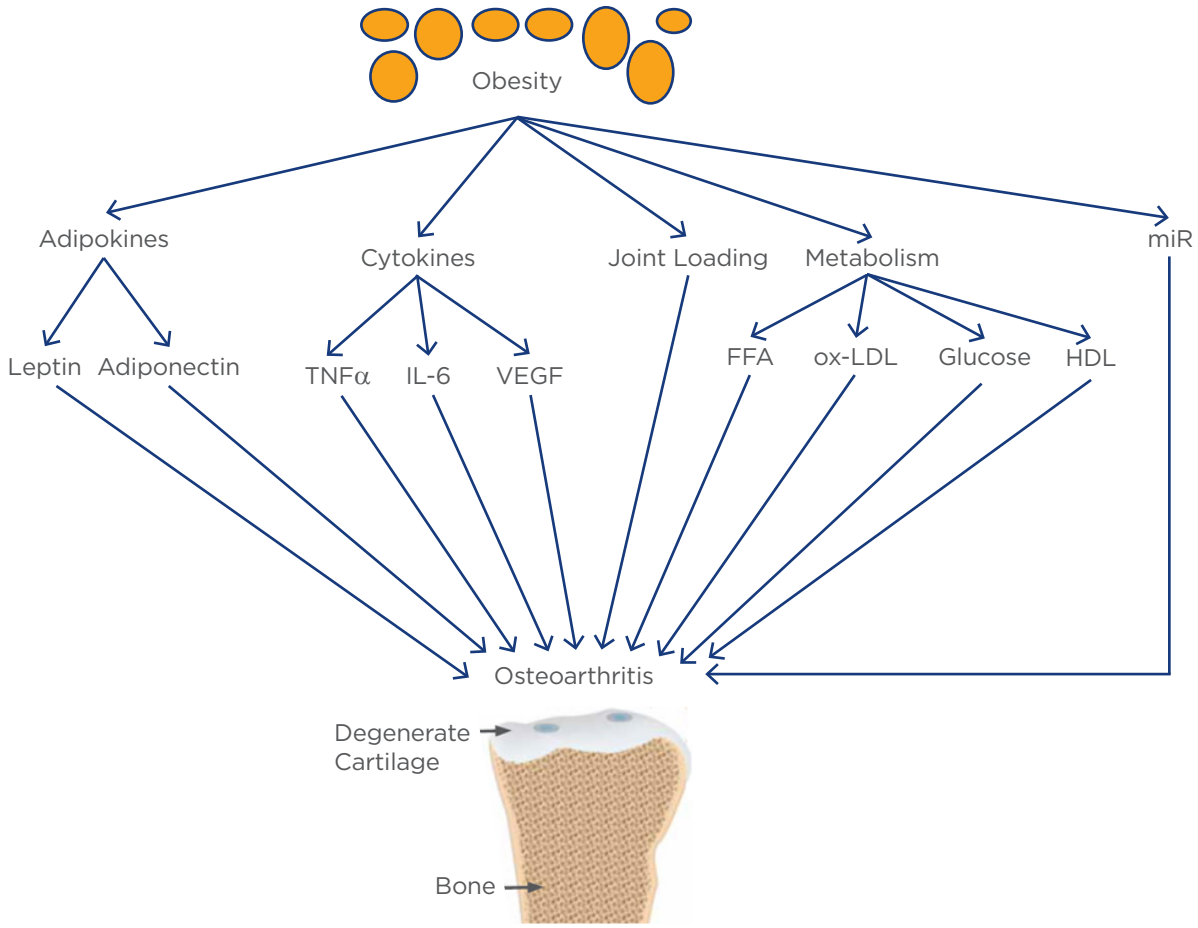

Figure 1: Proposed pathways linking obesity and osteoarthritis.
miR: microRNA; TNFα: tumour necrosis factor alpha; IL-6: interleukin-6; VEGF: vascular endothelial growth factor; FFA: free fatty acids; ox-LDL: oxidised low-density lipoprotein; HDL: high-density lipoprotein.

Levels of leptin in synovial fluid also correlate with BMI and severity of OA, and increased expression of the protein has been demonstrated in osteoarthritic cartilage when compared with normal cartilage.[24,25] Leptin appears to have a biphasic effect on cartilage, with low levels being physiologically important for normal cartilage synthesis and high levels contributing to cartilage degradation.[26] Serum leptin levels have been shown to correlate with both knee cartilage volume and thickness as assessed by magnetic resonance imaging (MRI) in cross-sectional studies.[27,28] In addition, a longitudinal study has demonstrated that both baseline serum leptin levels and changes in leptin levels are associated with changes in knee cartilage thickness.[27]

A further study demonstrated a relationship between higher serum leptin levels and increased development of cartilage defects, bone marrow lesions, synovitis, and effusions as assessed by MRI 10 years later.[29] The relationships between BMI, adiposity measurements, OA, and cartilage thickness appear to be mediated, at least in part, by leptin.[27,30] Leptin has also been shown to stimulate the secretion of inflammatory cytokines, including IL-6, from synovial fibroblasts, suggesting that it may play a role in synovial inflammation.[31] Subchondral osteoblasts overexpress leptin in OA patients and the associated abnormal osteoblast phenotype can be normalised by neutralisation of leptin.[32] Animal studies have shown that feeding mice a high-fat diet induces OA with corresponding increases in leptin, and that leptin levels correlate with severity of knee OA.[33,34] In contrast to these positive findings, a number of other studies have not reported an association between leptin and OA, particularly of the hand. A cross-sectional analysis of the NHANES III dataset revealed no association between serum leptin levels and hand OA.[35] This is supported by other studies in hand OA, which similarly report no association with serum leptin levels.[36,37]

A number of hypotheses have been proposed to explain these conflicting findings. The regulation of human energy stores, a system in which leptin is integral, is complex, with multiple interactions and feedback mechanisms. As with many homeostatic processes, a view that proposes a direct correlation between leptin and outcomes may be too simplistic. Leptin levels are pulsatile both throughout the day and with a relative nocturnal increase; measurements at a single timepoint may not provide an accurate reflection of functional leptin levels.[20,21] Leptin is interlinked with the hypothalamic—pituitary axis in the control of body energy stores and factors such as central leptin resistance and leptin tolerance appear to be important in the longer-term effects of this adipokine.[20] Most but not all human obesity appears to be associated with an insensitivity to leptin; 5-10% of obese humans have relatively low levels of leptin.[21] Again, this indicates a need for the development of a broader view of leptin functionality analogous to advances in the understanding of type 2 diabetes mellitus (T2DM). A further complication in the interpretation of leptin levels came with the realisation that not only did leptin not correlate directly with adipose tissue volume at an individual level, but there was also production of leptin in other body tissues such as skeletal muscle.[21] The inference from these findings is not that leptin is not important but rather that our understanding of the complex mechanisms governing its function is incomplete.

A further putative role for leptin in OA is as a pain modulator. Both serum and synovial fluid leptin levels have been shown to correlate with pain intensity in chronic OA.[37-39] In animal studies, the intra-articular administration of leptin has been associated with mixed findings. Bao et al.[40] found a predominantly catabolic effect with increased levels of matrix metalloproteinase (MMP)-2, MMP-9, cathepsin D, and collagen II with decreased basic fibroblast growth factor and depletion of proteoglycan in articular cartilage. In contrast, an earlier study by Dumond et al.[24] reported anabolic effects following intra-articular injection of leptin, with increased synthesis of insulin-like growth factor 1 and transforming growth factor beta 1 (TGF-β1). Our evolving understanding of the precise meanings behind changes in cytokine levels may explain some of these apparent discrepancies; for example, TGF-β has also been associated with the induction of OA-like changes.[41] Taken together, these data suggest that excess leptin has a negative effect on cartilage in the large joints of the lower limbs but not in the small, non-weight bearing joints of the hand. Some of the contribution to OA symptoms may be mediated through nociceptor effects. This makes leptin antagonists potentially interesting agents for therapeutic investigation in OA. Recombinant leptin and leptin analogues are now available for the treatment of congenital leptin deficiency and lipodystrophy.[20] However, no clinical studies of leptin antagonists in OA have been conducted

to date. The prohibitive cost of these agents is a significant hurdle to be overcome before their use in such a common disorder can be considered; currently available leptin analogues cost in excess of €500,000 per patient per year.

Adiponectin

Adiponectin is an intriguing 30-kDa adipokine because serum levels inversely correlate with BMI. Its physiological role demonstrates insulin-sensitising, anti-inflammatory, and anti-atherogenic properties.[20] Adiponectin levels are increased in OA but negatively correlate with pain and OA severity.[39,42-44] This suggests that adiponectin may play a protective role in OA. Worryingly, an association between increased adiponectin levels and both all-cause and cardiovascular (CV) mortality has been demonstrated.[45-47] This is despite the negative association of adiponectin and T2DM, and the association of the latter with CV and all-cause mortality.[48] The reasons behind, and the implications of, this apparently conflicting prognostic role for adiponectin are yet to be fully elucidated.[49] Chondrocyte studies have shown that adiponectin increases tissue inhibitor of MMP-2 and decreases IL-1β-induced MMP-13.[50] In contrast, other studies have shown that adiponectin can increase nitric oxide synthase 2, MMP-3, MMP-9, and IL-6.[51] Synovial fibroblast studies have shown increased IL-6 production when stimulated with adiponectin.[52] These apparent discrepancies in the laboratory data mirror the clinical confusion over the role of adiponectin in health and disease, and suggest that we do not yet fully understand this unusual adipokine. Adiponectin agonists are in development, with a goal of treating obesity-related diseases such as T2D. These include an oral small-molecule agonist that has been shown to prolong lifespan and ameliorate diabetes in a mouse model.[53] No such agents have yet been assessed in OA models.

Other Adipokines

Resistin, visfatin, and chemerin are the most studied of the plethora of other known adipokines. Resistin is a 12.5-kDa adipokine that is also expressed by macrophages.[54] Resistin levels are elevated in the synovial tissue of OA patients and intra-articular injection of resistin can induce arthritis in a mouse model.[55] Resistin upregulates gene expression and stimulates the synthesis of a large number of pro-inflammatory cytokines.[55] Visfatin has been shown to play an important catabolic role in human OA chondrocytes and in a mouse model of OA.[56] Chemerin levels in synovial fluid correlate with the severity of knee OA.[57] Chemerin expression in synovium and the infrapatellar fat pad is higher in OA patients than in normal individuals.[58]

CYTOKINES

In addition to adipokines, a number of other cytokines are released from adipose tissue. The major sources of these are the resident tissue macrophages and other immune cells. Three key cytokines that potentially play a role in OA and have been demonstrated to have increased expression or serum levels in obesity are TNFα, IL-6, and vascular endothelial growth factor (VEGF).[59-61]

Tumour Necrosis Factor Alpha

TNFα is a key cytokine in the inflammatory pathogenesis of rheumatoid arthritis (RA), and anti-TNFα agents are a key part of the rheumatologist's armamentarium in treating this disease. Expression of TNFα is elevated in obesity and decreases with weight loss.[59,60] While TNFα levels are elevated in OA, agents targeting this pathway have been disappointing in clinical studies to date.[62,63] Serum levels of TNFα are associated with knee cartilage loss.[62] Given the emerging understanding of the importance of synovial inflammation in the development of OA, a potential benefit from TNFα blockade is conceivable. It is possible that personalised treatment of OA based on clinical criteria and biomarkers, as has been proposed for RA, would improve outcomes. Further evaluation of patients with higher serum or synovial fluid TNFα levels, greater radiographic or arthroscopic demonstration of synovitis, or indeed obese patients in whom inflammatory change may play a greater role would all be of interest.

Interleukin-6

IL-6 is a pro-inflammatory cytokine for which both serum levels and adipose tissue expression are elevated in obesity.[60] It is proven to be important in the pathogenesis of RA and is targeted in clinical use by the IL-6 blocking agent tocilizumab.[64] Levels are elevated in the serum and synovial fluid in OA, and correlate with knee cartilage loss.[39,62] IL-6 has been shown to play an essential role in cartilage destruction in an animal model of OA.[65] As yet, no reports on the use of IL-6 blockade in

OA exist. Current evidence suggests that IL-6 might be a therapeutic target in OA, possibly by intra-articular administration.

Vascular Endothelial Growth Factor

VEGF is a cytokine and growth factor that is important in angiogenesis. VEGF inhibitors have been developed and are utilised in cancer treatment, as well as other indications. Serum VEGF levels correlate with BMI and are associated with visceral fat accumulation in obese individuals.[61] VEGF levels in serum and synovial fluid are increased in OA patients compared with healthy controls.[66,67] Synovial fluid VEGF levels correlate with radiographic and functional assessments of knee OA severity.[66] The VEGF-blocking agent bevacizumab has been shown to inhibit the development of post-traumatic OA in an animal model when administered locally or systemically.[68] These data are promising for the potential use of these agents in OA. However, a number of obstacles remain, including the evaluation of potential adverse events in this population and an economic evaluation of the benefit—cost ratio of such a treatment.

EPIGENETICS

A number of epigenetic mechanisms may play a role in OA and its links with obesity. The best studied of these are microRNA molecules (miRNAs). Other potentially important mechanisms include DNA methylation and histone acetylation.

MicroRNA

Studies of the human genome led to the discovery that only a small minority of the transcribed genome is ultimately translated into protein. The majority remains as noncoding RNA molecules. Initially regarded as 'junk DNA', the science of epigenetics has revealed the importance of these molecules in the regulation of gene expression. The miRNAs are a class of short (18-25 nucleotides), highly conserved, noncoding RNA molecules.[69] In terms of gene regulation, miRNAs have been shown to adjust the translational output of coding RNAs both by increasing their degradation and inhibiting RNA translation into protein.[69]

The importance of miRNA in a variety of diseases and pathogenic mechanisms is becoming increasingly evident.[69] It is likely that, as with genetics as a whole, they are important to some degree in almost all disease processes. Iliopoulos et al.[70] evaluated a panel of 365 miRNAs from the cartilage of patients undergoing surgery for OA and compared them with miRNAs from the cartilage of patients with no history of OA undergoing fracture surgery as a control group. They found significant changes in the levels of 16 miRNAs. These included both upregulation (miR-16, miR-22, miR-23b, miR-30b, miR-103, miR-223, miR-377, miR-483, miR-509), denoting a detrimental effect for the implicated miRNAs, and downregulation (miR-25, miR-26a, miR-29a, miR-140, miR-210, miR-337, miR-373), implying a protective effect. They also found that five of these miRNAs were associated with BMI (miR-22 and miR-103 positively, miR-25, miR-29a, and miR-337 negatively), suggesting a role for miRNAs in the link between obesity and OA pathogenesis. Other researchers confirmed the downregulation of miR-140 and reported the negative association of miR-146 and OA grade.[71,72]

A large number of other miRNAs are potentially of importance in OA pathogenesis, although not necessarily modulated through obesity, and our knowledge in this area is expanding rapidly.[73] Two miRNAs (miR-935 and miR-4772) have been shown to be upregulated in obese individuals who do not respond to a dietary intervention for weight loss.[74] Weight loss following bariatric surgery, but not diet-induced weight loss, has been shown to be associated with both upregulation (miR-221, miR-199a-3p) and downregulation (miR-16-1, miR-122, miR-140-5p, miR-193a-5p) of miRNAs.[75] Targeting miRNA either by using anti-miRNAs or by miRNA mimicry has emerged as a potential therapeutic option in pre-clinical studies.[69] Mimicry of miR-140 using double-stranded miR-140 demonstrated functional effects on OA-related genes, with upregulation of a disintegrin and metalloproteinase with thrombospondin motifs 5 (ADAMTS5) and downregulation of aggrecan.[71] Synthetic miR-146a suppresses extracellular matrix-associated proteins (MMP-13 and ADAMTS5) and IL-1-mediated induction of inflammatory markers (COX2, IL-8).[76]

Other Epigenetic Mechanisms

While undoubtedly important in OA pathogenesis, other epigenetic mechanisms potentially linking obesity and OA remain to be fully explored. Leptin expression has been shown to correlate with DNA methylation. In addition, Iliopoulos et al.[77] demonstrated the negative association of leptin

methylation in OA chondrocytes, as well as a role for histone acetylation in the leptin promoter.

MECHANICAL LOADING

Mechanical loading has the potential to alter joint biology in addition to its direct physical effects. Abnormal mechanical loading of resident chondrocytes increases the expression of catabolic factors such as MMPs, and decreases proteoglycan, DNA, and collagen synthesis.[78] In addition, increased loading can alter the chondrocyte inflammatory phenotype, with increased release of IL-1 and TNFα.[79] This combination of effects has the end result of predisposing the articular cartilage to a degradative state.

LIPID AND GLUCOSE METABOLISM

Abnormalities of lipid metabolism, in particular in relation to fatty acids and cholesterol, have been suggested to play an important role in the pathogenesis of OA. Lipid metabolic dysfunction is a characteristic of obesity, with increases in triglycerides, free fatty acids, and low-density lipoprotein (LDL) cholesterol, accompanied by a decrease in high-density lipoprotein (HDL) cholesterol.[79] Omega-3 polyunsaturated fatty acids (PUFAs) have a potential role in protection from OA through decreased production of inflammatory cytokines, free radicals, and eicosanoids.[80] An animal model of OA has demonstrated a protective effect of omega-3 PUFAs on OA development, which is in contrast to the increased synovitis, osteophytosis, and OA severity observed with increased saturated fatty acid consumption.[81] A clinical study in humans showed an association between a greater proportion of omega-3 PUFAs and protection from cartilage degradation, as well as increasing levels of synovitis with omega-6 PUFAs.[82] A mechanistic link between these fatty acid abnormalities and joint damage is suggested by the ability of free fatty acids to activate macrophages.[83]

Abnormalities in both HDL and oxidised (ox)-LDL have been linked to OA development. Reduced or dysfunctional HDL may contribute to OA. Serum HDL levels are reduced in patients with OA and increased HDL protects from the development of subchondral bone marrow lesions.[84,85] Animal studies with functional HDL-knockout mice fed a high-fat diet have shown increased rates of cartilage degradation and catabolic mediators.[86] Ox-LDL correlates with BMI and is found in OA synovial fluid.[87] Ox-LDL stimulates MMP release and decreases chondrocyte proteoglycan synthesis.[88] A murine model has demonstrated the ability of ox-LDL to increase synovitis, inflammatory mediators, and clinical arthritis, as well as a therapeutic potential for receptor blockade.[89] T2DM has been proposed as an independent risk factor for OA development.[90] Sustained hyperglycaemia results in a low-grade systemic inflammatory state and has direct deleterious effects on cartilage by inducing chondrocyte dysfunction and subchondral bone destruction.[91]

CONCLUSION

Both obesity and OA are increasing health problems in our society. While the major contributor to the increase in OA is related to an ageing population, obesity is mainly determined by diet and lifestyle. Both conditions share an important genetic component to their pathogenesis. Increasing evidence points towards a significant contribution of obesity to OA. This raises concerns of a 'knock-on' effect of the current obesity epidemic on future OA rates. Aside from biomechanics, the effects of obesity on OA are also likely to be mediated by a number of other factors including adipokines, cytokines, and miRNAs. Among adipokines, leptin and adiponectin are the most studied. Leptin appears to have a negative effect on OA, with increased levels being associated with more severe disease in most studies. Adiponectin's role appears more complicated, with increased levels found in OA patients but conflicting laboratory data on the functional effects of this adipokine. As in RA, cytokines appear to play a role in OA, at least in some patients, with the greatest evidence for TNFα, IL-6, and VEGF, all of which are overexpressed in individuals with obesity. Epigenetics, and miRNAs in particular, are an expanding science likely to be of relevance in OA pathogenesis. A number of different miRNAs appear to be either protective or harmful in OA. Our knowledge of these aspects of OA remains in its infancy, with no agents yet in clinical trials. Further exploration has the potential to open new frontiers in the management of this debilitating condition, which currently has no effective disease-modifying therapy.

REFERENCES

1. Cross M et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1323-30.

2. Dahaghin S et al. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). Ann Rheum Dis. 2005;64(5):682-7.

3. Murray CJ et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859): 2197-223.

4. Vos T et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859): 2163-96.

5. Piscitelli P et al. Socioeconomic burden of total joint arthroplasty for symptomatic hip and knee osteoarthritis in the Italian population: a 5-year analysis based on hospitalization records. Arthritis Care Res (Hoboken). 2012;64(9):1320-7.

6. Dahaghin S et al. Prevalence and determinants of one month hand pain and hand related disability in the elderly (Rotterdam study). Ann Rheum Dis. 2005;64(1):99-104.

7. Busija L et al. Osteoarthritis. Best Pract Res Clin Rheumatol. 2010;24(6):757-68.

8. Di Cesare PE et al., "Pathogenesis of Osteoarthritis," Firestein GS et al. (eds.), Kelley's Textbook of Rheumatology (2009) 8th edition, Philadelphia: Saunders Elsevier, pp. 1525-46.

9. Anderson JJ, Felson DT. Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol. 1988;128(1):179-89.

10. Rodriguez-Fontenla C et al. Assessment of osteoarthritis candidate genes in a meta-analysis of nine genome-wide association studies. Arthritis Rheumatol. 2014;66(4):940-9.

11. Ayral X et al. Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis -- results of a 1 year longitudinal arthroscopic study in 422 patients. Osteoarthritis Cartilage. 2005;13(5):361-7.

12. Spector TD, MacGregor AJ. Risk factors for osteoarthritis: genetics. Osteoarthritis Cartilage. 2004;12 Suppl A:S39-44.

13. Ng M et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9945):766-81.

14. Radin EL et al. Role of mechanical factors in pathogenesis of primary osteoarthritis. Lancet. 1972;1(7749): 519-22.

15. Carman WJ et al. Obesity as a risk factor for osteoarthritis of the hand and wrist: a prospective study. Am J Epidemiol. 1994;139:119-29.

16. Sowers MF et al. BMI vs. body composition and radiographically defined osteoarthritis of the knee in women: a 4-year follow-up study. Osteoarthritis Cartilage. 2008;16(3):367-72.

17. Ding C et al. Body fat is associated with increased and lean mass with decreased knee cartilage loss in older adults: a prospective cohort study. Int J Obes (Lond). 2013;37(6):822-7.

18. Wang Y et al. Relationship between body adiposity measures and risk of primary knee and hip replacement for osteoarthritis: a prospective cohort study. Arthritis Res Ther. 2009;11(2):R31.

19. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab. 2004;89:2548-56.

20. Blüher M, Mantzoros CS. From leptin to other adipokines in health and disease: facts and expectations at the beginning of the 21st century. Metabolism. 2015;64(1):131-45.

21. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature. 1998;395(6704):763-70.

22. Mantzoros CS et al. Leptin concentrations in relation to body mass index and the tumor necrosis factor-alpha system in humans. J Clin Endocrinol Metab. 1997;82(10):3408-13.

23. Staikos C et al. The association of adipokine levels in plasma and synovial fluid with the severity of knee osteoarthritis. Rheumatology (Oxford). 2013;52(6):1077-83.

24. Dumond H et al. Evidence for a key role of leptin in osteoarthritis. Arthritis Rheum. 2003;48(11):3118-29.

25. Ku JH et al. Correlation of synovial fluid leptin concentrations with the severity of osteoarthritis. Clin Rheumatol. 2009;28(12):1431-5.

26. Pottie P et al. Obesity and osteoarthritis: more complex than predicted! Ann Rheum Dis. 2006;65(11):1403-5.

27. Stannus OP et al. Cross-sectional and longitudinal associations between circulating leptin and knee cartilage thickness in older adults. Ann Rheum Dis. 2015;74(1):82-8.

28. Ding C et al. Association between leptin, body composition, sex and knee cartilage morphology in older adults: the Tasmanian older adult cohort (TASOAC) study. Ann Rheum Dis. 2008;67(9): 1256-61.

29. Karvonen-Gutierrez CA et al. The relationship between longitudinal serum leptin measures and measures of magnetic resonance imaging-assessed knee joint damage in a population of mid-life women. Ann Rheum Dis. 2014;73(5):883-9.

30. Fowler-Brown A et al. The mediating effect of leptin on the relationship between body weight and knee osteoarthritis in older adults. Arthritis Rheumatol. 2015;67(1):169-75.

31. Yang WH et al. Leptin induces IL-6 expression through OBRl receptor signaling pathway in human synovial fibroblasts. PLoS One. 2013;8(9):e75551.

32. Henrotin Y et al. Subchondral bone and osteoarthritis: biological and cellular aspects. Osteoporos Int. 2012;23 Suppl 8:S847-51.

33. Griffin TM et al. Induction of osteoarthritis and metabolic inflammation by a very high-fat diet in mice: effects of short-term exercise. Arthritis Rheum. 2012;64(2):443-53.

34. Griffin TM et al. Diet-induced obesity differentially regulates behavioral, biomechanical, and molecular risk factors for osteoarthritis in mice. Arthritis Res Ther. 2010;12(4):R130.

35. Massengale M et al. The relationship between hand osteoarthritis and serum leptin concentration in participants of the Third National Health and Nutrition Examination Survey. Arthritis Res Ther. 2012;14(3):R132.

36. Yusuf E et al. Association between leptin, adiponectin and resistin and long-term progression of hand osteoarthritis. Ann Rheum Dis. 2011;70(7):1282-4.

37. Massengale M et al. Adipokine hormones and hand osteoarthritis: radiographic severity and pain. PLoS One. 2012;7(10):e47860.

38. Lübbeke A et al. Do synovial leptin levels correlate with pain in end stage arthritis? Int Orthop. 2013;37(10):2071-9.

39. Bas S et al. Adipokines correlate with pain in lower limb osteoarthritis: different associations in hip and knee. Int Orthop. 2014;38(12):2577-83.

40. Bao JP et al. Leptin plays a catabolic role on articular cartilage. Mol Biol Rep. 2010;37(7):3265-72.

41. van Beuningen HM et al. Osteoarthritis-like changes in the murine knee joint

resulting from intra-articular transforming growth factor-beta injections. Osteoarthritis Cartilage. 2000;8(1):25-33.

42. Honsawek S, Chayanupatkul M. Correlation of plasma and synovial fluid adiponectin with knee osteoarthritis severity. Arch Med Res. 2010;41(8):593-8.

43. Laurberg TB et al. Plasma adiponectin in patients with active, early, and chronic rheumatoid arthritis who are steroid- and disease-modifying antirheumatic drug-naive compared with patients with osteoarthritis and controls. J Rheumatol. 2009;36(9):1885-91.

44. Louer CR et al. Diet-induced obesity significantly increases the severity of posttraumatic arthritis in mice. Arthritis Rheum. 2012;64(10):3220-30.

45. Sook Lee E et al. Association between adiponectin levels and coronary heart disease and mortality: a systematic review and meta-analysis. Int J Epidemiol. 2013;42(4):1029-39.

46. Forsblom C et al. Serum adiponectin concentration is a positive predictor of all-cause and cardiovascular mortality in type 1 diabetes. J Intern Med. 2011;270(4): 346-55.

47. Wu ZJ et al. Adiponectin is associated with increased mortality in patients with already established cardiovascular disease: a systematic review and meta-analysis. Metabolism. 2014;63(9):1157-66.

48. Li S et al. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2009;302(2): 179-88.

49. Kizer JR. Adiponectin, cardiovascular disease, and mortality: parsing the dual prognostic implications of a complex adipokine. Metabolism. 2014;63(9): 1079-83.

50. Chen TH et al. Evidence for a protective role for adiponectin in osteoarthritis. Biochim Biophys Acta. 2006;1762(8): 711-8.

51. Lago R et al. A new player in cartilage homeostasis: adiponectin induces nitric oxide synthase type II and pro-inflammatory cytokines in chondrocytes. Osteoarthritis Cartilage. 2008;16(9): 1101-9.

52. Tang CH et al. Adiponectin enhances IL-6 production in human synovial fibroblast via an AdipoR1 receptor, AMPK, p38, and NF-kappa B pathway. J Immunol. 2007;179(8):5483-92.

53. Okada-Iwabu M et al. A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. Nature. 2013;503(7477):493-9.

54. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol. 2006;6:772–83.

55. Zhang Z et al. Resistin induces expression of proinflammatory cytokines and chemokines in human articular chondrocytes via transcription and messenger RNA stabilization. Arthritis Rheum. 2010;62(7):1993-2003.

56. Yang S et al. NAMPT (visfatin), a direct target of hypoxia-inducible factor-2α, is an essential catabolic regulator of osteoarthritis. Ann Rheum Dis. 2013;doi:10.1136/annrheumdis-2013-204355. [Epub ahead of print].

57. Valcamonica E et al. Levels of chemerin and interleukin 8 in the synovial fluid of patients with inflammatory arthritides and osteoarthritis. Clin Exp Rheumatol. 2014;32(2):243-50.

58. Conde J et al. Differential expression of adipokines in infrapatellar fat pad (IPFP) and synovium of osteoarthritis patients and healthy individuals. Ann Rheum Dis. 2014;73(3):631-3.

59. Hotamisligil GS et al. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest. 1995;95(5):2409-15.

60. Kern PA et al. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab. 2001;280(5):E745-51.

61. Miyazawa-Hoshimoto S et al. Elevated serum vascular endothelial growth factor is associated with visceral fat accumulation in human obese subjects. Diabetologia. 2003;46(11):1483-8.

62. Stannus O et al. Circulating levels of IL-6 and TNF-α are associated with knee radiographic osteoarthritis and knee cartilage loss in older adults. Osteoarthritis Cartilage. 2010;18(11):1441-7.

63. Magnano MD et al. A pilot study of tumor necrosis factor inhibition in erosive/inflammatory osteoarthritis of the hands. J Rheumatol. 2007;34(6):1323-7.

64. Hashizume M et al. Tocilizumab, A Humanized Anti-IL-6R Antibody, as an Emerging Therapeutic Option for Rheumatoid Arthritis: Molecular and Cellular Mechanistic Insights. Int Rev Immunol. 2014;doi:10.3109/08830185.2014.938325. [Epub ahead of print].

65. Ryu JH et al. Interleukin-6 plays an essential role in hypoxia-inducible factor 2α-induced experimental osteoarthritic cartilage destruction in mice. Arthritis Rheum. 2011;63(9):2732-43.

66. Kim HR et al. The relationship between synovial fluid VEGF and serum leptin with ultrasonographic findings in knee osteoarthritis. Int J Rheum Dis. 2014;doi:10.1111/1756-185X.12486. [Epub ahead of print].

67. Mabey T et al. Angiogenic cytokine expression profiles in plasma and synovial fluid of primary knee osteoarthritis. Int Orthop. 2014;38(9):1885-92.

68. Nagai T et al. Bevacizumab, an anti-vascular endothelial growth factor antibody, inhibits osteoarthritis. Arthritis Res Ther. 2014;16(5):427.

69. Maegdefessel L. The emerging role of microRNAs in cardiovascular disease. J Intern Med. 2014;276(6):633-44.

70. Iliopoulos D et al. Integrative microRNA and proteomic approaches identify novel osteoarthritis genes and their collaborative metabolic and inflammatory networks. PLoS One. 2008;3(11):e3740.

71. Miyaki S et al. MicroRNA-140 is expressed in differentiated human articular chondrocytes and modulates interleukin-1 responses. Arthritis Rheum. 2009;60(9):2723-30.

72. Yamasaki K et al. Expression of MicroRNA-146a in osteoarthritis cartilage. Arthritis Rheum. 2009;60(4):1035-41.

73. Tsezou A. Osteoarthritis Year in Review 2014: genetics and genomics. Osteoarthritis Cartilage. 2014;22(12): 2017-24.

74. Milagro FI et al. High-throughput sequencing of microRNAs in peripheral blood mononuclear cells: identification of potential weight loss biomarkers. PLoS One. 2013;8(1):e54319.

75. Ortega FJ et al. Targeting the circulating microRNA signature of obesity. Clin Chem. 2013;59(5):781-92.

76. Li X et al. MicroRNA-146a is linked to pain-related pathophysiology of osteoarthritis. Gene. 2011;480(1-2):34-41.

77. Iliopoulos D et al. Epigenetic regulation of leptin affects MMP-13 expression in osteoarthritic chondrocytes: possible molecular target for osteoarthritis therapeutic intervention. Ann Rheum Dis. 2007;66(12):1616-21.

78. Fujisawa T et al. Cyclic mechanical stress induces extracellular matrix degradation in cultured chondrocytes via gene expression of matrix metalloproteinases and interleukin-1. J Biochem. 1999;125(5):966-75.

79. Thijssen E et al. Obesity and osteoarthritis, more than just wear and tear: pivotal roles for inflamed adipose tissue and dyslipidaemia in obesity-induced osteoarthritis. Rheumatology (Oxford). 2015;54(4):588-600.

80. Masuko K et al. A metabolic aspect of osteoarthritis: lipid as a possible contributor to the pathogenesis of cartilage degradation. Clin Exp Rheumatol. 2009;27(2):347-53.

81. Wu CL et al. Dietary fatty acid content regulates wound repair and the pathogenesis of osteoarthritis following joint injury. Ann Rheum Dis. 2014;doi:10.1136/annrheumdis-2014-205601. [Epub ahead

of print].

82. Baker KR et al. Association of plasma n-6 and n-3 polyunsaturated fatty acids with synovitis in the knee: the MOST study. Osteoarthritis Cartilage. 2012;20(5):382-7.

83. Nguyen MT et al. A subpopulation of macrophages infiltrates hypertrophic adipose tissue and is activated by free fatty acids via Toll-like receptors 2 and 4 and JNK-dependent pathways. J Biol Chem. 2007;282(48):35279-92.

84. Soran N et al. Assessment of paraoxonase activities in patients with knee osteoarthritis. Redox Rep. 2008;13(5):194-8.

85. Doré D et al. A longitudinal study of the association between dietary factors, serum lipids, and bone marrow lesions of the knee. Arthritis Res Ther. 2012;14(1):R13.

86. Triantaphyllidou IE et al. Perturbations in the HDL metabolic pathway predispose to the development of osteoarthritis in mice following long-term exposure to western-type diet. Osteoarthritis Cartilage. 2013;21(2):322-30.

87. Simopoulou T et al. Lectin-like oxidized low density lipoprotein receptor 1 (LOX-1) expression in human articular chondrocytes. Clin Exp Rheumatol. 2007;25(4):605-12.

88. Kakinuma T et al. Lectin-like oxidized low-density lipoprotein receptor 1 mediates matrix metalloproteinase 3 synthesis enhanced by oxidized low-density lipoprotein in rheumatoid arthritis cartilage. Arthritis Rheum. 2004;50(11):3495-503.

89. Ishikawa M et al. Lectin-like oxidized low-density lipoprotein receptor 1 signal is a potent biomarker and therapeutic target for human rheumatoid arthritis. Arthritis Rheum. 2012;64(4):1024-34.

90. Davies-Tuck ML et al. Increased fasting serum glucose concentration is associated with adverse knee structural changes in adults with no knee symptoms and diabetes. Maturitas. 2012;72(4):373-8.

91. Hiraiwa H et al. Inflammatory effect of advanced glycation end products on human meniscal cells from osteoarthritic knees. Inflamm Res. 2011;60(11):1039-48.

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DIFFUSE LARGE B CELL LYMPHOMA OF THE FOOT IN A PATIENT WITH RHEUMATOID ARTHRITIS

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ABSTRACT

Patients with rheumatoid arthritis (RA) have an increased risk of developing malignant lymphomas, especially non-Hodgkin's lymphoma (NHL). However, primary lymphoma in a joint is rare. Here we report a case of a 68-year-old man with a background of RA who presented with a 1-year history of pain and swelling in his right ankle. Initial imaging results comprised of X-ray and magnetic resonance imaging were inconclusive. Ultrasound scan of the right foot revealed a very large vascular mass with grossly eroded tarsal bones, and a biopsy confirmed the diagnosis of diffuse large B cell lymphoma. Involvement of lymphoma of ankle/foot joints is very rare: to our knowledge this is the first case of a primary diffuse large B cell lymphoma of the joints of the mid and hind foot with underlying bone destruction in a patient with a background of RA. This case is important because it highlights that malignancy should be suspected in every patient with a background of RA and unusual characteristics before assuming a diagnosis of flare of RA. This is important because early diagnosis of NHL can contribute to improved outcome.

Keywords: Rheumatoid arthritis, lymphoma, joint, malignancy.

BACKGROUND

We present a case of a 68-year-old man with a background of longstanding seropositive rheumatoid arthritis (RA), who presented with a 1-year history of pain and swelling in his right ankle. Plain radiographs were unremarkable and magnetic resonance imaging (MRI) findings were inconclusive. Ultrasound (US) scan of the right foot revealed a very large vascular mass with grossly eroded tarsal bones and a biopsy confirmed the diagnosis of diffuse large B cell lymphoma (DLBCL). RA has been associated with malignancy, including haematological disease, but joint-based lymphomas are very rarely reported. This case is important because it highlights that malignancy should be suspected in every patient with a background of RA and unusual characteristics before assuming a diagnosis of flare of RA. This is important because early diagnosis of non-Hodgkin's lymphoma (NHL) can contribute to improved outcome.

CASE PRESENTATION

A 68-year-old Caucasian male with a background of longstanding seropositive, erosive RA presented with a 2-month history of pain and swelling in his right ankle. He reported that there had been two preceding episodes of pain and swelling in the same joint during the previous year; both had lasted a few days and resolved spontaneously. There had been no history of trauma. He reported no problems with his other joints. He reported no symptoms suggestive of systemic disease; specifically, he denied fever, significant weight loss, and reported no history of longstanding night sweats. Past medical history was remarkable for asthma and osteoporosis. There was no personal history of hepatitis or tuberculosis, and no family history of

haematological malignancy. The patient was an ex-smoker who drank minimal alcohol socially. His RA was well controlled on methotrexate (MTX) 15 mg weekly and folic acid 5 mg weekly, and his other medications included an oral bisphosphonate, calcium and vitamin D supplements, and inhalers. He had required one course of oral steroids per year for exacerbations of asthma. He had seropositive (rheumatoid factor-positive) RA. Upon clinical examination, his right ankle was swollen and tender. There was no evidence of synovitis in any other peripheral joints. Lymphadenopathy, hepatomegaly, and splenomegaly were not found.

INVESTIGATIONS

The patient was initially investigated with blood tests and imaging in the form of radiographs and subsequent MRI. The blood test results, including full blood count and renal and liver profiles, were unremarkable apart from mildly elevated inflammatory markers (erythrocyte sedimentation rate: 22; C-reactive protein: 25). Plain radiographs of the right ankle and foot indicated a pathological process, with an initial suspicion of avascular necrosis of the navicular bone (Figure 1A). Further investigations of the right foot with MRI revealed bone marrow changes involving the talus, navicular, cuneiforms, cuboid, and the base of the fourth metatarsal with associated soft tissue component in the medial aspect of the mid/hind foot junction (Figure 1B). There was no effusion or evidence of erosions.

The differential diagnosis for these appearances was wide, including changes due to RA, infection, neuropathic joint, and tumour. Chest radiograph showed airway disease-associated changes only, with a stable appearance for 4 years. At this time, support of the foot with an Aircast® boot and follow-up was arranged, but no biopsy was undertaken. However, at follow-up 4 months later, the pain and swelling of the right foot had gradually worsened, warranting further investigations. Worryingly, new symptoms included weight loss, lethargy, and reduced appetite. There was no fever or night sweats. Upon examination there was a palpable right inguinal lymph node, but no hepatosplenomegaly, and the patient had developed a superficial ulcer on the right foot, a swab from which grew *Staphylococcus aureus* and which required treatment with antibiotics. In view of the clinical deterioration, US scan of the right ankle/foot and US-guided biopsy was arranged. The US scan of the right foot revealed a very large vascular mass that extended all the way around the tendons and involved the ankle and hind-foot joints, with grossly eroded tarsal bones (Figure 1C and Figure 1D).

HISTOLOGY

The biopsy showed infiltration by pleomorphic lymphocytes that were positive for CD20 and CD79a, which confirmed a B cell lineage (Figure 1E, Figure 1F). The atypical cells were also positive for CD23, BCL-2, and BCL-6. The proliferation fraction, as assessed by Ki-67 staining, was high (40-50%) (Figure 1G). The morphological and immunohistochemical findings supported a diagnosis of DLBCL.

TREATMENT

Urgent hospital admission was arranged and the patient was referred to the oncology team. Blood tests revealed hypercalcaemia (Ca [adjusted]: 3.22 mmol/l) and new renal impairment (urea: 8.0 mmol/l; creatinine: 140 µmol/l). A staging computed tomography scan of the neck, chest, abdomen, and pelvis revealed a large (88 × 54 mm) right inguinal nodal mass and a 12 mm external iliac node. A bone-marrow biopsy showed no evidence of involvement with NHL. A course of chemotherapy was initiated and the patient began a regimen of cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab; MTX was stopped at the time of chemotherapy. After completion of six cycles of chemotherapy with good partial response, the patient underwent radical consolidation radiotherapy. At follow-up, his ankle remained mildly swollen and painful, but the patient was well and in remission from his lymphoma.

DISCUSSION

RA has been associated with malignancy, including haematological disease, but joint-based lymphomas are very rarely reported, with only seven reports in the global case-report literature.[1-7] The musculoskeletal system is affected in up to 25% of patients diagnosed with NHL, although true articular signs such as joint swelling are less frequent and have been reported only rarely at the onset of NHL.[8] DLBCL represents the most frequent type of lymphoma and accounts for

approximately 25% of all NHL in the developed world. In the whole of Europe, the incidence is approximately 4.92 cases per 100,000 persons per year. Similar to most other NHLs, there is a male predominance, but it is less pronounced than for other subtypes of haematological malignancy. In a recent report from the Haematological Malignancy Research Network, the male/female DLBCL sex ratio was 1.13 (95% confidence interval [CI]: 1.01-1.26).[9] Incidence increases with age and the median age at presentation is 70.4 years for patients as a whole.[9]

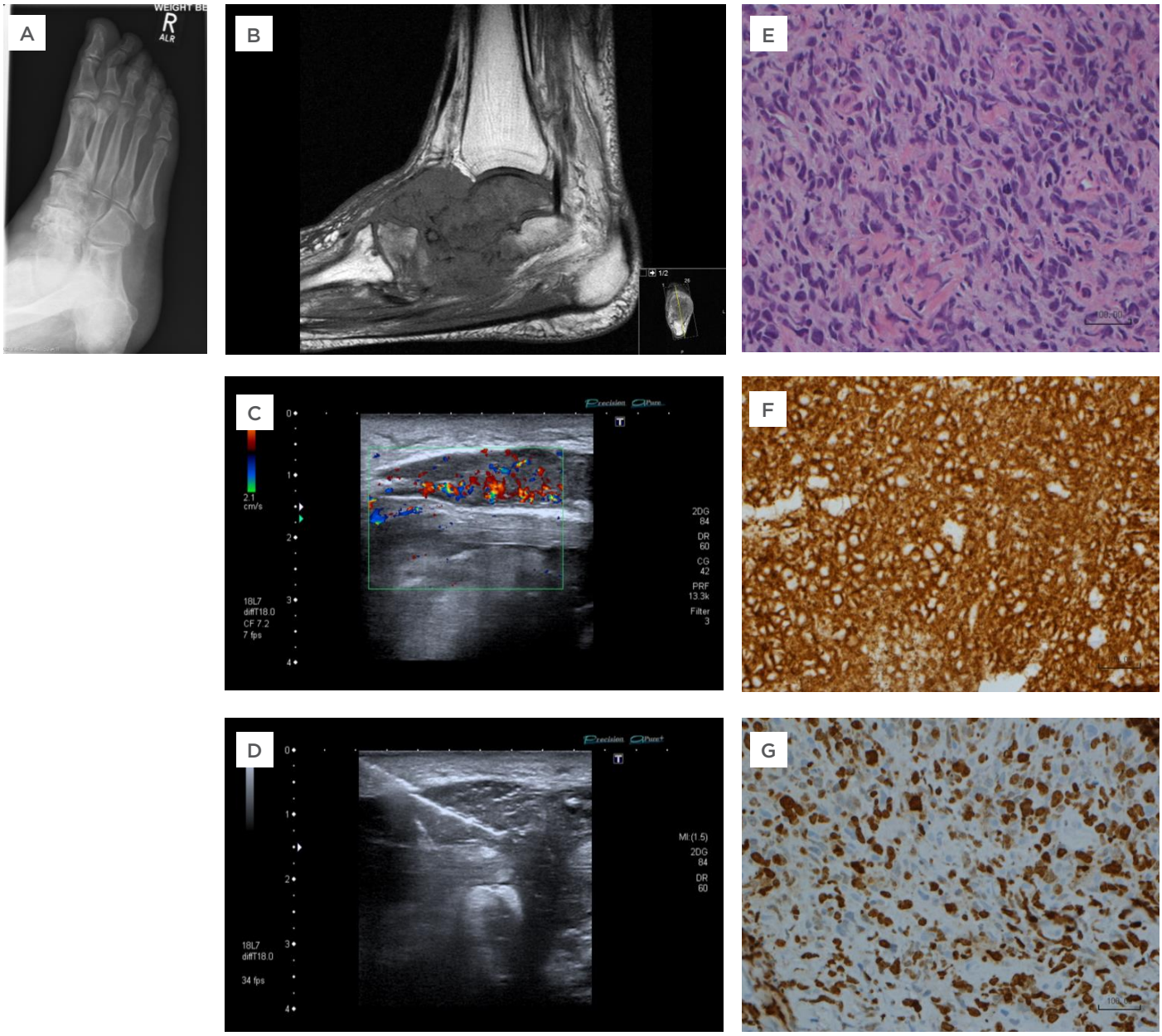

Figure 1: Radiology and histopathology images.
(A) Oblique radiograph of the right foot showing sclerosis and erosion of the talus, navicular, and medial cuneiform bones with soft tissue swelling. (B) Sagittally oriented image on 1.5 T Siemens Symphony magnetic resonance imaging scanner on T1 weighting showing the extent of the soft tissue mass invading the talus, navicular, calcaneum, and cuboid bones and crossing the sinus tarsi. (C and D) High-resolution ultrasound image with colour Doppler using a Toshiba 17 MHz linear probe showing extensive, highly vascular soft tissue enveloping the tibialis posterior tendon; and image demonstrating the ultrasound-guided needle biopsy passing into the soft tissue mass. (E) Foot-mass biopsy showing diffuse infiltrate of large cells with mitotic activity. (F) Tumour cells showing strong staining of CD20. (G) Ki-67 stain showing high proliferation fraction.

Patients with DLBCL typically present with a mass that has a rapid growth rate and which causes symptoms when it infiltrates tissues or obstructs organs (most commonly nodal enlargement in the neck or abdomen or, in the case of primary mediastinal large B cell lymphoma, the mediastinum) but it may present as a mass lesion anywhere in the body. However, DLBCL may present with only joint pain or swelling, even in the presence of normal haematological findings. If the primary presentation manifests as arthritis, the most common site of involvement is the knee.[1,2,10-12] Other reported sites have been the shoulder, elbow, metacarpophalangeal and sternoclavicular joint, and as a polyarticular presentation, and these often mimic inflammatory arthritis.[6-8,13-17] Several other reports have identified the involvement of lymphoma of the ankle/foot joints, but not specifically in patients with known RA.[17-22] The only other reported case involving lymphoma of the ankle/foot joints in a patient with RA demonstrated a primary tumour of the synovium without bony involvement.[23]

To the best of our knowledge this is the first case of a primary DLBCL of the joints of the mid and hind foot with underlying bone destruction in a patient with a background of RA. However, the association between RA and lymphoma has been well documented. Lymphoproliferative disorders occur with increased frequency in patients with RA: incidence and mortality rates due to leukaemia or lymphoma are approximately 2-fold higher than expected. The results of a meta-analysis suggest that RA patients have an approximately 2-fold increase in lymphoma risk compared with the general population (standardised incidence ratio: 2.08, 95% CI: 1.80-2.39).[24] Lymphoma incidence increases as active RA persists, and correlates with the severity of disease activity.[25] A recent review shows that aggressive B cell lymphomas, particularly the DLBCL as seen in the present case, are more strongly associated with autoimmune rheumatic diseases than more indolent lymphomas.[26] Although the presence of NHL is less strongly associated with RA than with Sjögren's syndrome and systemic lupus erythematosus, a 28-fold increased risk of NHL in patients with RA has been reported in severe destructive RA.[26]

The main pathophysiological mechanisms of NHL are B cell hyperactivity and chronic inflammation.[26] In RA, the rheumatic disease itself appears to have a larger effect on the development of lymphoma than its therapy.[25] However, there remains uncertainty as to the causative factor of RA-associated lymphoma. It remains possible that drugs used to treat the disease through alteration of immune function and immunological surveillance may contribute to the risk. This concern has been applied to medications such as azathioprine, MTX, and anti-tumour necrosis factor alpha therapy.[27] In addition, discontinuation of MTX has been followed by disappearance of lymphoma in some patients.[27] In a meta-analysis investigating the risk of lymphoma development in autoimmune diseases, the subgroup analyses for the studies using cytotoxic drugs, including MTX, show that the random effects standardised incidence rate for NHL in RA was 5.1 (95% CI: 0.9-28.6).[28]

The case of our patient represents a diagnostic challenge not only because of the rarity of the condition but also due to the presentation of the disease without symptoms usually associated with a malignant condition. The presence of a monoarthritis in a patient with known RA can suggest several alternative diagnoses, such as monoarticular flare of RA, pigmented villonodular synovitis, and synovial chondromatosis. Moreover, several non-rheumatological diseases can present with musculoskeletal involvement coexisting with RA, especially infection and malignancy. Both need to be excluded early in the course of the disease in order to avoid errors in diagnosis, inappropriate treatment, and possible serious complications. In conclusion, malignancy must be suspected in every patient with a history of RA and unusual characteristics before assuming a diagnosis of flare of RA.

REFERENCES

1. Visser J et al. Non-Hodgkin's lymphoma of the synovium discovered in total knee arthroplasty: a case report. BMC Res Notes. 2012;5:449.

2. Chim CS et al. EBV-associated synovial lymphoma in a chronically inflamed joint in rheumatoid arthritis receiving prolonged methotrexate treatment. Haematologica. 2006;91(8 Suppl):ECR31.

3. George DA et al. Large B cell lymphoma of the subtalar and talonavicular joint synovium. BMJ Case Rep. 2013;doi:10.1136/bcr-2012-007683.

4. De Angelis F et al. Atypical presentation of anaplastic large T-cell

lymphoma mimicking an articular relapse of rheumatoid arthritis in a patient treated with etanercept. A case report and literature review. Leuk Res. 2012;36(9):e199-201.

5. Gordon MJ et al. Lymphoma of the hands in a patient with rheumatoid arthritis: case report. J Hand Surg Am. 2014;39(4):728-31.

6. Kennedy JW et al. An unusual presentation of methotrexate-induced B-cell lymphoma of the metacarpophalangeal joint: a case report and literature review. J Hand Surg Am. 2006;31(7):1193-6.

7. Arredondo J et al. Non-Hodgkin's lymphoma as an unexpected diagnosis in a shoulder arthroplasty. J Arthroplasty. 1999;14(1):108-11.

8. Dorfman HD et al. Non-Hodgkin's lymphoma of the synovium simulating rheumatoid arthritis. Arthritis Rheum. 1987;30(2):155-61.

9. Smith A et al. Incidence of haematological malignancy by sub-type: a report from the Haematological Malignancy Research Network. Br J Cancer. 2011;105(11):1684-92.

10. Jamieson KA et al. Synovial presentation of non-Hodgkin's lymphoma. Br J Radiol. 1998;71(849):980-2.

11. Khan SY, Hutchinson DG. Primary synovial non-Hodgkin's lymphoma in association with ankylosing spondylitis. Rheumatology (Oxford). 2004;43(3):391.

12. Haase KK et al. Non-Hodgkin's lymphoma presenting as knee monoarthritis with a popliteal cyst. J Rheumatol. 1990;17(9):1252-4.

13. Jawa A et al. Primary intra-articular non-Hodgkin's lymphoma of the elbow. A case report. J Bone Joint Surg Am. 2006;88(12):2730-4.

14. Neri R et al. Case report. Elbow monoarthritis revealing B cell non-Hodgkin's lymphoma. Clin Rheumatol. 2013;32 Suppl 1:S111-4.

15. Adunsky A et al. Malignant lymphoma presenting as sternoclavicular joint arthritis. Arthritis Rheum. 1980;23(11): 1330-1.

16. Birlik M et al. Articular, B-cell, non-Hodgkin's lymphoma mimicking rheumatoid arthritis: synovial involvement in a small hand joint. Rheum Int. 2004;24(3):169-72.

17. Menon N, Madhok R. Symmetrical polyarthritis is not always rheumatoid. Ann Rheum Dis. 1994;53(10):631-2.

18. Gokdemir G et al. Primary cutaneous diffuse large B-cell lymphoma of the leg, with an atypical clinical picture of verrucous plaques associated with stasis dermatitis. Clin Exp Dermatol. 2010;35(3):e87-9.

19. Ramanujam CL et al. Cutaneous non-Hodgkin's lymphoma of the foot: a rare case report. J Foot Ankle Surg. 2009;48(5):581-4.

20. Singh DP et al. Primary lymphoma of the bones of the foot: management of two cases. Foot Ankle. 1991;11(5):314-6.

21. Nickisch F et al. Primary malignant non-Hodgkin lymphoma of the talus: a case report. Foot Ankle Int. 2005;26(7):568-71.

22. Mendeszoon MJ, Wire KR. Diffuse large B-cell lymphoma of the ankle: a case study of surgical intervention and outcome. J Am Podiatr Med Assoc. 2010;100(6):505-10.

23. Blume P et al. Case report and review of primary bone diffuse large B-cell lymphoma involving the calcaneus. J Foot Ankle Surg. 2013;52(5):666-72.

24. Smitten AL et al. Meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res Ther. 2008;10(2):R45.

25. Baecklund E et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006;54(3):692-701.

26. Dias C, Isenberg DA. Susceptibility of patients with rheumatic diseases to B-cell non-Hodgkin lymphoma. Nat Rev Rheumatol. 2011;7(6):360-8.

27. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum. 2004;50(6):1740-51.

28. Zintzaras E et al. The risk of lymphoma development in autoimmune diseases: a meta-analysis. Arch Intern Med. 2005;165(20):2337-44 .

DECIPHERING ECTOPIC CALCIFICATION: CONTRIBUTION OF THE RARE, INHERITED DISORDER PSEUDOXANTHOMA ELASTICUM

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ABSTRACT

Soft connective tissue calcification is still an intriguing problem due to the high number of genes, proteins, and enzymes involved in the process. Numerous epidemiological and experimental studies of the ectopic calcification associated with metabolic, inflammatory, and degenerative disorders have been performed. Moreover, in the last decade, great efforts have been made in studying the genetic disorders leading to soft connective tissue calcification, trying to understand the imbalance between pro and anti-calcifying factors in the different disorders, and why calcification occurs only in certain body regions (which often differ between the various genetic defects). The rare, inherited disorder pseudoxanthoma elasticum (PXE), which is caused by mutations in the *ABCC6* gene, is an interesting model because the gene responsible is mainly expressed in the liver, whereas calcification affects peripheral soft connective tissues. It has been suggested that liver deficiency of the protein encoded by *ABCC6* directly induces peripheral calcification, although, in contrast, several studies both in humans and in transgenic mice indicate that peripheral mesenchymal cells might be permanently involved in PXE calcification. In this review, the author suggests that early in development PXE cells may undergo epigenetic changes and acquire a permanent pro-calcific signature. However, given the complexity of the calcification process and the metabolic inter-exchanges among the different calcific genetic disorders, a bioinformatic approach analysing data ranging from genes to functional proteins and clinical features may complete the puzzle and provide new therapeutic perspectives in PXE, as well as in other calcific disorders.

Keywords: Soft connective tissue calcification, ectopic calcification, extracellular matrix calcification, fibroblast gene expression, fibroblast epigenetic changes, calcification genetic disorders, pseudoxanthoma elasticum.

SCIENTIFIC BACKGROUND

Soft connective tissue calcification is frequently observed in metabolic or degenerative/inflammatory processes, such as diabetes, chronic kidney disease, and atherosclerosis,[1-3] or within necrotic materials, such as in advanced atherosclerosis and tuberculosis.[4,5] The process has also been induced in animals and in cells *in vitro* via treatment with chemicals[6,7] or excess vitamins[8,9] in order to understand the metabolic pathways involved. Interestingly, mesenchymal cells were shown to switch to pro-osteogenic gene expression under the influence of various stimuli.[8,10,11] In the previous decade, great advances have been derived from studies on genetic disorders characterised by soft connective tissue calcification.

THE CALCIFICATION PROCESS AND ITS CONTROL

Calcification is due to the precipitation of minerals, the most abundant of which is calcium phosphate, followed by magnesium phosphate, and then calcium carbonate and magnesium carbonate.[12-14] Therefore, ectopic calcification is mainly due to hydroxyapatite accumulation. Within cells, free calcium works as a metabolic controller and its low

concentration (about 100-200 nmol/dm^3) is finely regulated by specific calcium-binding proteins.[15-17] Moreover, mitochondria and the endoplasmic reticulum can actively accumulate an excess of calcium in order to maintain intracellular ion homeostasis.[15,16,18] In contrast, calcium concentration in the extracellular space is physiologically very high (about 1 mmol/dm^3),[16,18] and it would form hydroxyapatite in the presence of phosphate, the level of which is, hopefully, finely regulated.[19] Therefore, the concentration of free phosphate can be considered as the limiting factor for extracellular matrix calcification.

Despite the various historical names, there are two main types of calcification: 'passive' and 'active'. Passive calcification is a consequence of metabolic, hormonal alterations,[1-3,7,12] or, more frequently, of cell degeneration and death.[5,20,21] In these cases, the intracellular and extracellular concentrations of free calcium and phosphate become high enough to overcome their solubility, with the formation of the rather insoluble form of calcium phosphate. Very high intracellular ion concentrations can be reached by alteration of the cell membrane barrier[12] due to deficiency in cellular ion-binding proteins and compartments,[16,18] or by the enzymatic liberation of ions, including phosphate derived from nucleic acids and the membrane phospholipids of dead cells.[22] High extracellular ion concentrations may be reached in kidney and hormonal disorders, or by erroneous diets.[1-3,7,8] Moreover, similar to calcification associated with atheroma or tuberculosis,[1,4,5] vessels are scarce in necrotic areas and ions remain sequestered for a long time, which favours the formation of large mineral precipitates. However, modification of the expression of genes involved in the homeostatic control of ion solubility has also been reported in cases of 'passive calcification'.[9,10,23,24] This is not surprising because months or even years are necessary in order to produce clinically relevant calcification, and time-dependent, adaptable gene expression of surviving cells can occur.

Active calcification is a dynamic process that occurs in the extracellular space of soft connective tissues in the absence of metabolic, inflammatory, or necrotic events. This process is very often age-associated and depends on the imbalance of proteins and enzymes that maintain the homeostatic control of calcium and phosphate ion concentrations within the extracellular space. Interestingly, some molecules exhibit opposing functions within bone and in soft connective tissues, as they seem to favour calcification within bone and yet inhibit calcium precipitation in the non-bone connective tissues.[25-29] Interestingly, calcification of soft connective tissues *in vivo* is often associated with, or dependent upon, osteoporotic bone decalcification.[25]

GENES AND PROTEINS INVOLVED IN ECTOPIC CALCIFICATION

Exhaustive reviews describing proteins involved in ectopic calcification have been published recently.[24,26,27] Some of these proteins, such as osteopontin[28] and fetuin,[29] mainly function within the extracellular fluids and inhibit calcification by interfering with crystal growth. Other proteins are involved in the regulation of extracellular ion concentrations at a local level, such as ectoenzyme nucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), progressive ankylosis protein (ANK), tissue non-specific alkaline phosphatase (TNAP), matrix Gla protein (MGP), and many others. While all of these proteins and enzymes have specific functions, they also form a functional network whose overall result depends on the polymorphisms and expression of their encoding genes, which are often influenced by environmental factors such as the surrounding matrix. This network is complex and only partially known, with inhibition of the expression of one gene inducing over or under-expression of other genes also involved in the calcification process.[25-27,30]

CONTRIBUTION OF GENETIC DISORDERS TO THE COMPREHENSION OF ECTOPIC CALCIFICATION

In recent years, studies on rare genetic disorders characterised by soft connective tissue calcification have greatly improved our knowledge of the mineralisation process.[26,31-33] For the majority of these diseases, the causative gene is known and transgenic mice are available, often recapitulating, at least in part, the clinical features present in humans. However, even when calcification is a direct consequence of a gene defect, the tissue-specific 'interpretation' of each single gene, either normal or mutated, is far from being completely understood.

A typical form of soft connective tissue calcification occurs in generalised arterial calcification of infancy (GACI), which is a rare genetic disorder caused

by loss of function in the gene encoding the enzyme ENPP1 that hydrolyses adenosine triphosphate to adenosine monophosphate and pyrophosphate (PPi). GACI is therefore characterised by systemic deficiency of the strong anti-calcifying factor PPi within the extracellular space.[34-36] This induces severe calcification of peri-articular tissues and arteries, which leads to heart failure, even possibly within the first months of life.[35,36] It is noteworthy that PPi inhibits the expression of pro-calcifying genes[37] and inhibits calcification because it binds hydroxyapatite and hinders crystal growth.[38] The strong effect of PPi deficiency in GACI suggests that, among the various anti-calcifying molecules, PPi must play a fundamental role, at least in vessels, peri-articular tissues, and cartilage. Recently, the important role of PPi in calcification has been confirmed by the observation that surviving GACI patients may present clinical and histological features typical of another rare genetic disorder, pseudoxanthoma elasticum (PXE), which is characterised by skin, retina, and vessel calcification,[39] and in which matrix calcification is associated with, or dependent upon, a series of peripheral cell metabolic alterations, among which is high TNAP activity and consequent deficiency of extracellular PPi.[40-42] Apart from PPi, TNAP liberates phosphate from a variety of organic molecules, including ATP, phospholipids, and even the DNA of necrotic cells.[43] The expression of TNAP is complex, is regulated by circulating and local factors, and its activity produces high levels of pro-calcific free phosphate.[44,45]

Within the extracellular matrix, PPi and inorganic phosphate are always in a dynamic equilibrium determined by the activity of enzymes, kidney function, hormones, and diet. Generalised calcification due to a high level of phosphate is present in chronic kidney disorders,[46] with alteration of gene expression towards bone-specific phenotypes.[48,49] Interestingly, administration of PPi is able to reduce calcification in haemodialysed patients, uraemic mice, and *in vitro* cells.[49,50] Therefore, the level of PPi must be kept relatively high in peripheral soft connective tissues in order to avoid calcification. This is also influenced by the activity of ANK, which transports PPi from within cells to the extracellular space.[51] The low level of extracellular PPi present in cases of ANK deficiency induces calcification of the articular cartilage and dysregulation of osteoblastic/osteoclastic differentiation, as seen in humans and in transgenic mice.[52,53] ANK deficiency further confirms the importance of PPi as an anti-calcifying factor in the extracellular matrix, but also stresses the importance of tissue-specific gene expression for the maintenance of appropriate levels of PPi within the extracellular milieu of different body regions.

Another important anti-calcifying molecule is the mature form of MGP. MGP deficiency, both in humans[54] and in transgenic mice,[31] has demonstrated the importance of glutamic-acid-rich proteins within the extracellular space.[55] In particular, MGP seems to prevent calcium precipitation within vessel walls and within peripheral soft connective tissues due to its ion-binding capability[56] and also due to its interaction with extracellular matrix molecules that have a relevant role in calcification.[57] As shown in both humans and transgenic mice, mutations in the *MGP* gene may lead to a loss of expression or deficient maturation of the protein, which causes a decrease in its anti-calcifying potential. MGP is actively produced by fibroblasts and smooth muscle cells, and seems to regulate calcification at a local level, although it is present within the systemic circulation.[58] Moreover, the activity of MGP depends on its post-transcriptional maturation, i.e. γ-carboxylation of glutamic acid residues and phosphorylation of serine residues.[59] These events are governed by specific genes and may also depend on exogenous factors such as vitamin K.[60] Indeed, a study on another human genetic disorder characterised by severe calcification of skin (vitamin K epoxide reductase [VKOR] deficiency), showed that MGP deficiency may be due to impairment of the vitamin K cycle, which produces the reduced form of vitamin K necessary for γ-carboxylation and maturation of MGP.[61] In addition, calcification in humans may also depend on the ability of the microRNA molecule miR-133a to regulate expression of VKOR complex subunit 1.[62] These data once again illustrate the complex interdependence of genes and environmental factors in the calcification process.

Low amounts of mature, γ-carboxylated MGP have also been observed in PXE, which is characterised by calcification of elastic fibres within soft connective tissues.[63,64] Fibroblasts isolated from the dermis of PXE patients produce a low amount of γ-carboxylated MGP *in vitro*.[65] Interestingly, this immature form of MGP is strongly associated with calcified elastic fibres in the dermis of PXE patients.[66] Low levels of MGP were also observed

in the ATP-binding cassette, subfamily C member 6 (*Abcc6*) −/− model of PXE.[67] Therefore, MGP seems to play an important role in the calcification process caused by ABCC6/*Abcc6* deficiency. Given the importance of vitamin K to MGP maturation, this vitamin was thought to be directly involved in PXE calcification and this was supported by the low level of vitamin K measured in PXE patients.[68] However, studies on transgenic mice[69] and on fibroblasts *in vitro*[70] failed to confirm a role for vitamin K in PXE-associated MGP maturation. Interestingly, data from PXE fibroblasts *in vitro* showed that vitamins K1 and K2 increase cellular protein carboxylation, with the exception of MGP.[71] However, given the recent observation that vitamin K administration reduces mineralisation in zebrafish models of PXE and GACI,[72] the role of vitamin K and of vitamin K-dependent MGP expression and maturation should be investigated further in both humans and animal models.

CONTRIBUTION OF PSEUDOXANTHOMA ELASTICUM TO THE UNDERSTANDING OF ECTOPIC CALCIFICATION

The current review describes data derived from studies on plasma and *in vitro* fibroblasts isolated from the dermis of PXE patients obtained in our laboratory through the use of various techniques, from molecular biology and gene expression to metabolic and structural analyses. PXE is an interesting model for studying the calcification process. It is a recessive inherited disorder caused by mutations in the gene *ABCC6*, which encodes a protein that is a member of the ATP-binding cassette (ABC) family of membrane transporters, mainly expressed in the liver and kidney and much less in other tissues.[73] Its role is to export substances directly or indirectly involved in calcification out of hepatocytes. PXE is characterised by progressive calcification of elastic fibres, mainly in the medium dermis (Figure 1), in vessel walls, and in Bruch's membrane within the retina (Figure 2).[39,40,63,64] These organs are located far from the liver, kidney, and other major gene-expressing tissues,[73] and therefore it is reasonable to accept that plasma from PXE patients is deficient in anti-calcific molecules produced and secreted by the liver,[71] or that peripheral cells, such as smooth muscle cells and fibroblasts, modify their metabolism towards a more pro-calcifying phenotype as a consequence of liver ABCC6 deficiency.[40,41,74]

The substrates of the protein encoded by *ABCC6* are still under investigation: it has been suggested that leukotriene C4, organic anions, and glutathione conjugates, as well as synthetic compounds, could be substrates.[75,76] Data obtained through molecular docking and virtual-screening approaches indicate that lipids are also potential substrates for ABCC6.[77] Recent data suggest that ABCC6 mediates the release of ATP from hepatocytes,[78] with mutations in the transporter leading to low plasma levels of ATP-derived, anti-calcific PPi. Interestingly, a deficiency in circulating ATP would be in agreement with the markers of oxidative stress observed in the plasma of PXE patients[79] and in *Abcc6* −/− mice,[80] as well as with the low peripheral level of anti-calcifying PPi due to the low level of substrate available for ENPP1.[34-36] Less clear, and more indirect, is the effect of plasma ATP deficiency on proteoglycan,[81,82] lipoprotein, and triglyceride[83,84] alterations that we and other groups have observed in PXE patients, as well as in *Abcc6* −/−transgenic mice.

Deficiency in the poorly identified circulating factors produced by the liver is suggested to favour peripheral calcification in PXE.[71] Indeed, we and other laboratories have observed that the serum of PXE patients has an abnormal composition compared with age-matched controls because it has a redox potential lower than normal, high levels of oxidised proteins and lipids,[79] and an abnormal amount and quality of glycosaminoglycans,[82] lipoproteins, triglycerides,[84] and proteins that may directly interfere with calcium precipitation, such as fetuin A.[29,85,86] These alterations *in vivo* may depend on the specific genotype of the PXE patient. However, higher levels of cholesterol and triglycerides, as well as reduced levels of fetuin A, have been measured in transgenic mice that differ only in the ablation of the *Abcc6* gene.[83,86] Therefore, all of the plasma alterations observed in PXE patients, with the majority being confirmed in *Abcc6* −/− transgenic mice, may be the result of an age-dependent adjustment of a series of interdependent genes whose modified expression is due to a loss of function in ABCC6. Moreover, as PXE is a genetic disorder, these alterations would probably start during embryogenesis and therefore profoundly and permanently influence mesenchymal cell metabolism and differentiation.[87]

A B

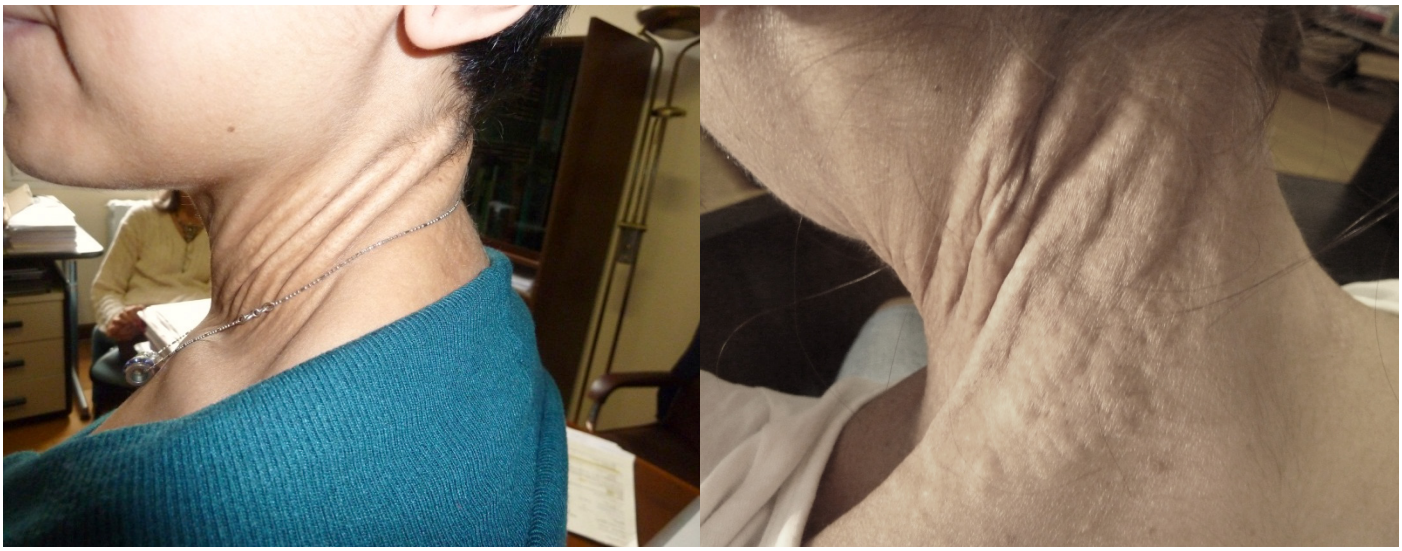

Figure 1: Skin alterations in the neck of a 17-year-old girl (A) and a 35-year-old woman (B) affected by pseudoxanthoma elasticum.
The elastic fibre calcification within the dermis produces confluent papules and redundant skin in the affected areas.

A B

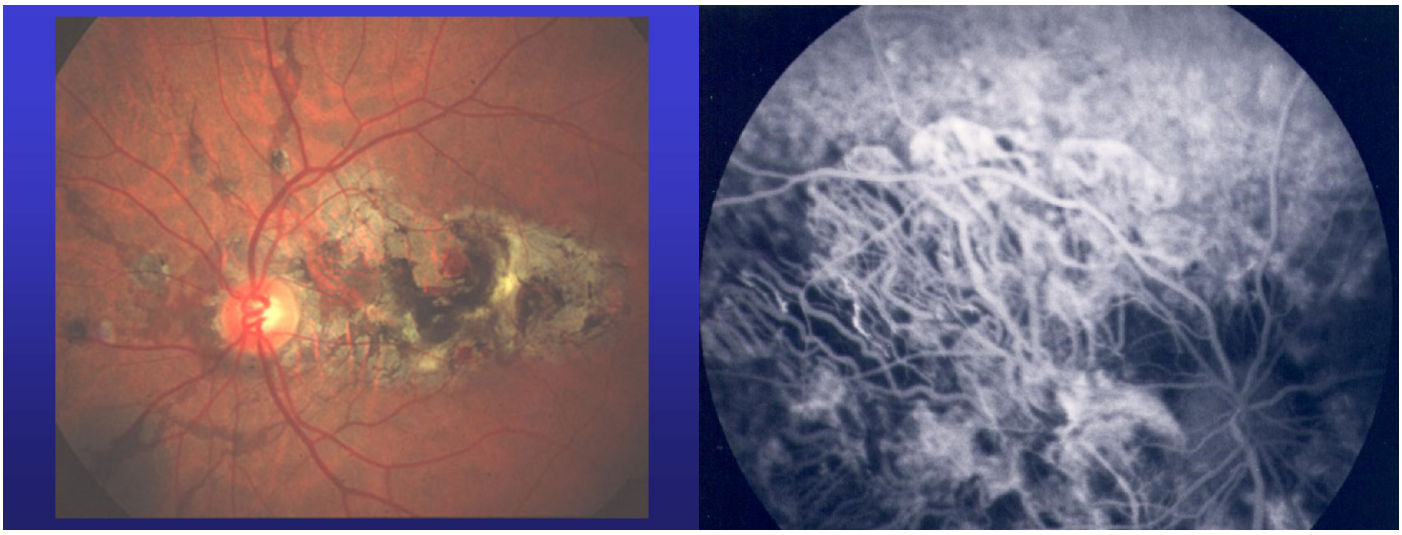

Figure 2: The retina of a 45-year-old man (A) and a 45-year old woman (B) affected by pseudoxanthoma elasticum.
Displaying great heterogeneity between patients, calcification of the elastin in Bruch's membrane induces angioid streaks, followed by neovascularisation, haemorrhages, and scarring.

Several studies have shown that fibroblasts isolated from the dermis of PXE patients exhibit metabolic behaviour and gene expression that is different from sex and age-matched controls. Some alterations are evident only in the absence of fetal calf serum,[84] suggesting that PXE fibroblast metabolism *in vivo* is continuously influenced by circulating factors.[79,80,82,83,85,86] However, several of these metabolic alterations have been shown in PXE fibroblasts grown in optimal culture conditions *in vitro*, which suggests an intrinsic and permanent abnormal gene expression in these cells.[41,65,66,70,74,81,84,88-92] Moreover, some of these metabolic alterations have also been observed

in *Abcc6* −/− transgenic mice,[67,80] confirmed in fibroblasts isolated from these animals and which exhibit a pro-calcific phenotype *in vitro*,[93] and have also been shown in ABCC6-knockdown HepG2 cells.[94] Therefore, data from patients and from animal models of PXE, as well as data from fibroblasts isolated from patients and from transgenic mice, strongly indicate that ABCC6 deficiency induces generalised and local metabolic alterations that are largely independent from circulating factors, and that are permanent and transmissible to subsequent generations because they can be observed up to the 8th passage *in vitro*. In contrast, the onset and severity of clinical manifestations would seem to depend on the genetic background of the patients and mice,[95-97] on the interplay among membrane transporter genes and their promoters,[76,98,99] and on unrelated metabolic disorders.[100-102]

CONCLUSION AND PERSPECTIVES

Studies on calcifying genetic disorders have largely contributed to solving the puzzle of identifying the genes and proteins involved in calcification. In some cases, calcification is due to the mutation of genes controlling the production of anti-calcifying molecules, such as PPi in GACI due to *ENPP1* mutations, or carboxylated MGP in gamma-glutamyl carboxylase or VKOR deficiencies. The case of PXE is more complex, involving calcification of peripheral soft connective tissues,[63,64,73] whereas the protein encoded by the mutated gene (whose function is still not clear) is mainly expressed in the liver. Recent data indicate ATP as the substrate exported by the ABCC6 transporter from within hepatocytes into the circulation.[78] This finding would explain some of the plasma alterations we and others have observed in PXE, but it would not explain the permanent metabolic alterations observed in isolated fibroblasts in the presence of normal calf serum, such as deficient MGP carboxylation,[65-68] redox imbalance,[70,91,92] altered proteoglycan metabolism,[81,82] higher matrix degradation,[88,89] membrane transporter alterations,[90] altered lipoprotein and cholesterol metabolism,[83,84] and expression of a pro-calcific phenotype.[41,42,65,68,74,93]

In conclusion, the data on PXE patients, isolated fibroblasts, and animal models seem to indicate that: i) Extracellular matrix calcification in PXE depends on *ABCC6* mutations (causative), genetic background (affecting onset and severity), and environmental factors (nature of surrounding matrix, diet, age); ii) PXE fibroblasts maintained in optimal culture conditions *in vitro* exhibit a permanent pro-calcific gene expression profile without expressing genes involved in osteogenesis,[41] which is also confirmed in fibroblasts isolated from *Abcc6* −/− mice;[93] iii) This peculiar and permanent gene expression profile of PXE fibroblasts could depend on permanent epigenetic modifications of genes, promoters, or histones, as a consequence of *ABCC6* mutations during embryogenesis or early in development. This hypothesis is supported by the fact that epigenetic regulation of *ABCC6* gene expression has already been observed,[98,99] and that *in vitro* fibroblasts isolated from normal and *Abcc6* −/− mice with identical genetic background show different pro-calcific phenotypes;[93] iv) The 'epigenetic' proposal for the 'pro-calcific' signature of PXE fibroblasts could explain the peculiar organ distribution of calcification, as it has been shown that fibroblasts very quickly differentiate depending on the area of migration and maintain the acquired differentiation throughout their lifespan;[87,103] v) Given the great influence of environmental factors on epigenetic events, this hypothesis may also explain the different clinical phenotypes and severities among PXE patients, even in the presence of identical *ABCC6* mutations and a similar/identical genetic background, as in identical twins; vi) Identification of epigenetic modulation of gene expression in PXE peripheral cells could open new therapeutic perspectives for PXE and other calcification disorders. To conclude, the enormous amount of data derived from studies on PXE and on other inherited calcific disorders strongly indicate that a bioinformatic approach ranging from genes to proteins and to clinical features could help to identify the crucial, and probably common, steps towards calcification upon which therapeutic approaches can be based.

REFERENCES

1. Kramer CK et al. Coronary artery calcium score prediction of all causes mortality and cardiovascular events in people with type 2 diabetes: systematic review and meta-analysis. BMJ. 2013;346:f1654.
2. Cox AJ et al. Contributors to mortality

in high-risk diabetic patients in the Diabetes Heart Study. Diabetes Care. 2014;37(10):2798-803.

3. Stompór T. Coronary artery calcification in chronic kidney disease: An update. World J Cardiol. 2014;6(4):115-29.

4. Hayashi K et al. Putty lung: pulmonary parenchymal calcification due to tuberculosis. Jpn J Radiol. 2012;30(1): 92-3.

5. Kara I et al. Panoramic radiographic appearance of massive calcification of tuberculous lymph nodes. J Contemp Dent Pract. 2008;9(6):108-14.

6. Doyle DV et al. Potassium permanganate induced calcergy: a model to study the effects of drugs on hydroxyapatite crystal deposition. J Pathol. 1979;128(2):63-9.

7. Zhou Y et al. Overexpression of c1q/ tumor necrosis factor-related protein-3 promotes phosphate-induced vascular smooth muscle cell calcification both in vivo and in vitro. Arterioscler Thromb Vasc Biol. 2014;34(5):1002-10.

8. Han MS et al. Functional cooperation between vitamin D receptor and Runx2 in vitamin D-induced vascular calcification. PLoS One. 2013;8(12):e83584.

9. Huk DJ et al. Increased dietary intake of vitamin A promotes aortic valve calcification in vivo. Arterioscler Thromb Vasc Biol. 2013;33(2):285-93.

10. Cui RR et al. MicroRNA-204 regulates vascular smooth muscle cell calcification in vitro and in vivo. Cardiovasc Res. 2012;96(2):320-9.

11. Aniket et al. Early osteoblast responses to orthopedic implants: Synergy of surface roughness and chemistry of bioactive ceramic coating. J Biomed Mater Res A. 2014;doi:10.1002/jbm.a.35326.

12. Giacomelli F et al. A study of metastatic renal calcification at the cellular level. J Cell Biol. 1964;22:189-206.

13. Eidelman N et al. Microstructure and mineral composition of dystrophic calcification associated with the idiopathic inflammatory myopathies. Arthritis Res Ther. 2009;11(5):R159.

14. Addison WN et al. Extracellular matrix mineralization in murine MC3T3-E1 osteoblast cultures: An ultrastructural, compositional and comparative analysis with mouse bone. Bone. 2015;71:244-56.

15. Carafoli E, Lehninger AL. A survey of the interaction of calcium ions with mitochondria from different tissues and species. Biochem J. 1971;122(5):681-90.

16. Rizzuto R et al. Ca(2+) transfer from the ER to mitochondria: when, how and why. Biochim Biophys Acta. 2009;1787: 1342-51.

17. Bakowski D et al. Endoplasmic reticulum-mitochondria coupling: local Ca^{2+} signalling with functional consequences. Pflugers Arch. 2012;464(1):27-32.

18. Brini M et al. Calcium in health and disease. Met Ions Life Sci. 2013;13:81-137.

19. Michigami T. Extracellular phosphate as a signaling molecule. Contrib Nephrol. 2013;180:14-24.

20. Lockard VG, Bloom S. Morphologic features and nuclide composition of infarction-associated cardiac myocyte mineralization in humans. Am J Pathol. 1991;139(3):565-72.

21. Mineda K et al. Chronic inflammation and progressive calcification as a result of fat necrosis: the worst outcome in fat grafting. Plast Reconstr Surg. 2014;133(5):1064-72.

22. Ciesiołka J et al. Antibiotic bacitracin induces hydrolytic degradation of nucleic acids. Biochim Biophys Acta. 2014;1840(6):1782-9.

23. Sen SK et al. Identification of candidate genes involved in coronary artery calcification by transcriptome sequencing of cell lines. BMC Genomics. 2014;15:198.

24. Evrard S et al. Vascular calcification: from pathophysiology to biomarkers. Clin Chim Acta. 2015;438:401-14.

25. Bucay N et al. Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes Dev. 1998;12(9):1260-8.

26. Rutsch F et al. Genetics in arterial calcification: pieces of a puzzle and cogs in a wheel. Circ Res. 2011;109(5):578-92.

27. Li Q, Uitto J. Mineralization/anti-mineralization networks in the skin and vascular connective tissues. Am J Pathol. 2013;183(1):10-8.

28. Hunter GK. Role of osteopontin in modulation of hydroxyapatite formation. Cal Tissue Int. 2013;93(4):348-54.

29. Brylka L, Jahnen-Dechent W. The role of fetuin-A in physiological and pathological mineralization. Cal Tissue Int. 2013;93(4):355-64.

30. Zeng Q et al. Augmented osteogenic responses in human aortic valve cells exposed to oxLDL and TLR4 agonist: a mechanistic role of Notch1 and NF-κB interaction. PLoS One. 2014;9(5):e95400.

31. Luo G et al. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. Nature. 1997;386(6620):78-81.

32. Kurosu H et al. Suppression of aging in mice by the hormone Klotho. Science. 2005;309(5742):1829-33.

33. Johnson K et al. Chondrogenesis mediated by PPi depletion promotes spontaneous aortic calcification in NPP1-/- mice. Arterioscler Thromb Vasc Biol. 2005;25(4):686-91.

34. Lomashvili KA et al. Vascular calcification is dependent on plasma levels of pyrophosphate. Kidney Int. 2014;85(6):1351-6.

35. Rutsch F et al. Mutations in ENPP1 are associated with 'idiopathic' infantile arterial calcification. Nat Genet. 2003;34(4):379-81.

36. Mackenzie NC et al. New insights into NPP1 function: lessons from clinical and animal studies. Bone. 2012;51(5):961-8.

37. Addison WN et al. Pyrophosphate inhibits mineralization of osteoblast cultures by binding to mineral, up-regulating osteopontin, and inhibiting alkaline phosphatase activity. J Biol Chem. 2007;282(21):15872-83.

38. Moreno EC et al. Pyrophosphate adsorption onto hydroxyapatite and its inhibition of crystal growth. Compend Suppl. 1987;(8):S256-8, S260, S262-6.

39. Li Q et al. Cutaneous features of pseudoxanthoma elasticum in a patient with generalized arterial calcification of infancy due to a homozygous missense mutation in the ENPP1 gene. Br J Dermatol. 2012;166(5):1107-11.

40. Nitschke Y, Rutsch F. Generalized arterial calcification of infancy and pseudoxanthoma elasticum: two sides of the same coin. Front Genet. 2012;3:302.

41. Boraldi F et al. Fibroblasts from patients affected by Pseudoxanthoma elasticum exhibit an altered PPi metabolism and are more responsive to pro-calcifying stimuli. J Dermatol Sci. 2014;74(1):72-80.

42. Dabisch-Ruthe M et al. Pyrophosphates as a major inhibitor of matrix calcification in Pseudoxanthoma elasticum. J Dermatol Sci. 2014;75(2):109-20.

43. Fedde KN, Whyte MP. Alkaline phosphatase (tissue-nonspecific isoenzyme) is a phosphoethanolamine and pyridoxal-5′-phosphate ectophosphatase: normal and hypophosphatasia fibroblast study. Am J Hum Genet. 1990;47(5):767-75.

44. Gan XT et al. CD73-TNAP crosstalk regulates the hypertrophic response and cardiomyocyte calcification due to α1 adrenoceptor activation. Mol Cell Biochem. 2014;394(1-2):237-46.

45. Escalante-Alcalde D et al. Retinoic acid and methylation cis-regulatory elements control the mouse tissue non-specific alkaline phosphatase gene expression. Mech Dev. 1996;57(1):21-32.

46. Nishizawa Y et al. Hyperphosphatemia and vascular calcification in end-stage renal disease. J Ren Nutr. 2005;15(1): 178-82.

47. Moe SM et al. Uremia induces the osteoblast differentiation factor Cbfa1 in human blood vessels. Kidney Int. 2003;63(3):1003-11.

48. Rong S et al. Vascular calcification

in chronic kidney disease is induced by bone morphogenetic protein-2 via a mechanism involving the Wnt/β-catenin pathway. Cell Physiol Biochem. 2014;34:2049-60.

49. Lomashvili KA et al. Reduced plasma pyrophosphate levels in hemodialysis patients. J Am Soc Nephrol. 2005;16(8):2495-500.

50. Riser BL et al. Daily peritoneal administration of sodium pyrophosphate in a dialysis solution prevents the development of vascular calcification in a mouse model of uraemia. Nephrol Dial Transplant. 2011;26(10):3349-57.

51. Morava E et al. Autosomal recessive mental retardation, deafness, ankylosis, and mild hypophosphatemia associated with a novel ANKH mutation in a consanguineous family. J Clin Endocrinol Metab. 2011;96(1):E189-98.

52. Kim HJ et al. Progressive ankylosis protein (ANK) in osteoblasts and osteoclasts controls bone formation and bone remodeling. J Bone Miner Res. 2010;25(8):1771-83.

53. Chen IP et al. A Phe377del mutation in ANK leads to impaired osteoblastogenesis and osteoclastogenesis in a mouse model for craniometaphyseal dysplasia (CMD). Hum Mol Genet. 2011;20(5):948-61.

54. Munroe PB et al. Mutations in the gene encoding the human matrix Gla protein cause Keutel syndrome. Nat Genet. 1999;21(1):142-4.

55. Viegas CS et al. Gla-rich protein acts as a calcification inhibitor in the human cardiovascular system. Arterioscler Thromb Vasc Biol. 2015;35(2):399-408.

56. O'Young J et al. Matrix Gla protein inhibits ectopic calcification by a direct interaction with hydroxyapatite crystals. J Am Chem Soc. 2011;133(45):18406-12.

57. Yao Y et al. Proline and gamma-carboxylated glutamate residues in matrix Gla protein are critical for binding of bone morphogenetic protein-4. Circ Res. 2008;102(9):1065-74.

58. Murshed M et al. Extracellular matrix mineralization is regulated locally; different roles of two gla-containing proteins. J Cell Biol. 2004;165(5):625-30.

59. Cranenburg EC et al. The circulating inactive form of matrix Gla Protein (ucMGP) as a biomarker for cardiovascular calcification. J Vasc Res. 2008;45(5): 427-36.

60. Schurgers LJ et al. Matrix Gla-protein: the calcification inhibitor in need of vitamin K. Thromb Haemost. 2008;100(4):593-603.

61. Oldenburg J et al. Vitamin K epoxide reductase complex subunit 1 (VKORC1): the key protein of the vitamin K cycle. Antioxid Redox Signal. 2006;8(3-4): 347-53.

62. Pérez-Andreu V et al. miR-133a regulates vitamin K 2,3-epoxide reductase complex subunit 1 (VKORC1), a key protein in the vitamin K cycle. Mol Med. 2013;18:1466-72.

63. Truter S et al. Calcification of elastic fibers in pseudoxanthoma elasticum. Mt Sinai J Med. 1996;63(3-4):210-5.

64. Pasquali-Ronchetti I et al. Pseudoxanthoma elasticum. Biochemical and ultrastructural studies. Dermatologica. 1981;163(4):307-25.

65. Boraldi F et al. Matrix gla protein and alkaline phosphatase are differently modulated in human dermal fibroblasts from PXE patients and controls. J Invest Dermatol. 2013;133(4):946-54.

66. Gheduzzi D et al. Matrix Gla protein is involved in elastic fiber calcification in the dermis of pseudoxanthoma elasticum patients. Lab Invest. 2007;87(10):998-1008.

67. Li Q et al. Pseudoxanthoma elasticum: reduced gamma-glutamyl carboxylation of matrix gla protein in a mouse model (Abcc6-/-). Biochem Biophys Res Commun. 2007;364(2):208-13.

68. Vanakker OM et al. Low serum vitamin K in PXE results in defective carboxylation of mineralization inhibitors similar to the GGCX mutations in the PXE-like syndrome. Lab Invest. 2010;90(6): 895-905.

69. Jiang Q et al. Administration of vitamin K does not counteract the ectopic mineralization of connective tissues in Abcc6 (-/-) mice, a model for pseudoxanthoma elasticum. Cell Cycle. 2011;10(4):701-7.

70. Boraldi F et al. Fibroblast protein profile analysis highlights the role of oxidative stress and vitamin K recycling in the pathogenesis of pseudoxanthoma elasticum. Proteomics Clin Appl. 2009;3(9):1084-98.

71. Le Saux O et al. Serum factors from pseudoxanthoma elasticum patients alter elastic fiber formation in vitro. J Invest Dermatol. 2006;126(7):1497-505.

72. Mackay EW et al. Vitamin K reduces hypemineralisation in zebrafish models of PXE and GACI. Development. 2015; 142(6):1095-101.

73. Matsuzaki Y et al. Tissue-specific expression of the ABCC6 gene. J Invest Dermatol. 2005;125(5):900-5.

74. Ronchetti I et al. Fibroblast involvement in soft connective tissue calcification. Front Genet. 2013;4:22.

75. Belinsky MG et al. Characterization of the drug resistance and transport properties of multidrug resistance protein 6 (MRP6, ABCC6). Cancer Res. 2002;62(21):6172-7.

76. Iliás A et al. Loss of ATP-dependent transport activity in pseudoxanthoma elasticum-associated mutants of human ABCC6 (MRP6). J Biol Chem. 2002;277(19):16860-7.

77. Hosen MJ et al. Molecular docking simulations provide insights in the substrate binding sites and possible substrates of the ABCC6 transporter. PLoS One. 2014;9(7):e102779.

78. Jansen RS et al. ABCC6-mediated ATP secretion by the liver is the main source of the mineralization inhibitor inorganic pyrophosphate in the systemic circulation-brief report. Arterioscler Thromb Vasc Biol. 2014;34(9):1985-9.

79. Garcia-Fernandez MI et al. Parameters of oxidative stress are present in the circulation of PXE patients. Biochim Biophys Acta. 2008;1782(7-8):474-81.

80. Li Q et al. Pseudoxanthoma elasticum: oxidative stress and antioxidant diet in a mouse model (Abcc6-/-). J Invest Dermatol. 2008;128(5):1160-4.

81. Passi A et al. Proteoglycan alterations in skin fibroblast cultures from patients affected with pseudoxanthoma elasticum. Cell Biochem Funct. 1996;14(2):111-20.

82. Götting C et al. Elevated xylosyltransferase I activities in pseudoxanthoma elasticum (PXE) patients as a marker of stimulated proteoglycan biosynthesis. J Mol Med (Berl). 2005;83(12):984-92.

83. Guo H et al. Atorvastatin counteracts aberrant soft tissue mineralization in a mouse model of pseudoxanthoma elasticum (Abcc6$^{-/-}$). J Mol Med (Berl). 2013;91(10):1177-84.

84. Kuzaj P et al. ABCC6- a new player in cellular cholesterol and lipoprotein metabolism? Lipids Health Dis. 2014;13:118.

85. Hendig D et al. Role of serum fetuin-A, a major inhibitor of systemic calcification, in pseudoxanthoma elasticum. Clin Chem. 2006;52(2):227-34.

86. Jiang Q et al. Overexpression of fetuin-a counteracts ectopic mineralization in a mouse model of pseudoxanthoma elasticum (abcc6(-/-)). J Invest Dermatol. 2010;130(5):1288-96.

87. Chang HY et al. Diversity, topographic differentiation, and positional memory in human fibroblasts. Proc Natl Acad Sci U S A. 2002;99(20):12877-82.

88. Gordon SG et al. Evidence for increased protease activity secreted from cultured fibroblasts from patients with pseudoxanthoma elasticum. Connect Tissue Res. 1978;6(1):61-8.

89. Quaglino D et al. Dermal fibroblasts from pseudoxanthoma elasticum patients have raised MMP-2 degradative potential. Biochim Biophys Acta. 2005;1741(1-2): 42-7.

90. Boraldi F et al. Multidrug resistance protein-6 (MRP6) in human dermal fibroblasts. Comparison between

cells from normal subjects and from Pseudoxanthoma elasticum patients. Matrix Biol. 2003;22(6):491-500.

91. Pasquali-Ronchetti I et al. Oxidative stress in fibroblasts from patients with pseudoxanthoma elasticum: possible role in the pathogenesis of clinical manifestations. J Pathol. 2006;208(1): 54-61.

92. Kuzaj P et al. Large-scaled metabolic profiling of human dermal fibroblasts derived from pseudoxanthoma elasticum patients and healthy controls. PLoS One. 2014;9(9):e108336.

93. Boraldi F et al. Changes in dermal fibroblasts from Abcc6(-/-) mice are present before and after the onset of ectopic tissue mineralization. J Invest Dermatol. 2014;134(7):1855-61.

94. Miglionico R et al. Dysregulation of gene expression in ABCC6 knockdown HepG2 cells. Cell Mol Biol Lett. 2014;19(4):517-26.

95. Zarbock R et al. Pseudoxanthoma elasticum: genetic variations in antioxidant genes are risk factors for early disease onset. Clin Chem. 2007;53(10):1734-40.

96. Li Q, Uitto J. The mineralization phenotype in Abcc6 (-/-) mice is affected by Ggcx gene deficiency and genetic background--a model for pseudoxanthoma elasticum. J Mol Med (Berl). 2010;88(2):173-81.

97. Boraldi F et al. Can ApoE and MTHFR polymorphisms have an influence on the severity of cardiovascular manifestations in Italian Pseudoxanthoma elasticum affected patients? Mol Gen Met Report. 2014;1:477-82.

98. Douet V et al. DNA methylation and Sp1 binding determine the tissue-specific transcriptional activity of the mouse Abcc6 promoter. Biochem Biophys Res Commun. 2007;354(1):66-71.

99. de Boussac H et al. The ERK1/2-hepatocyte nuclear factor 4alpha axis regulates human ABCC6 gene expression in hepatocytes. J Biol Chem. 2010;285(30):22800-8.

100. Hamlin N et al. Acquired Pseudoxanthoma elasticum-like syndrome in beta-thalassaemia patients. Br J Haematol. 2003;122(5):852-4.

101. Martin L et al. A mouse model of β-thalassemia shows a liver-specific down-regulation of Abcc6 expression. Am J Pathol. 2011;178(2):774-83.

102. Lau WL et al. Chronic kidney disease results in deficiency of ABCC6, the novel inhibitor of vascular calcification. Am J Nephrol. 2014;40(1):51-5.

103. Rinn JL et al. Anatomic demarcation by positional variation in fibroblast gene expression programs. PLoS Genet. 2006;2(7):e119.

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AXIAL SPONDYLOARTHRITIS: AN EVOLVING CONCEPT

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ABSTRACT

Axial spondyloarthritis (AxSpA) is the prototype of a family of inter-related yet heterogeneous diseases sharing common clinical and genetic manifestations: the spondyloarthritides (SpAs). The condition mainly affects the sacroiliac joints and axial skeleton, and has a clear classification scheme, wider epidemiological data, and distinct therapeutic guidelines when compared with other SpAs. However, the concept of AxSpA has not been immutable over time and has evolved tremendously on many levels over the past decades. This review identifies the evolution of the AxSpA concept at two levels. First, at the level of classification, the old classifications and rationales leading to the current Assessment of SpondyloArthritis international Society (ASAS) classification are reviewed, and the advantages and drawbacks are discussed. Second, at the therapeutic level, current and future treatments are described and treatment strategies are discussed.

Keywords: Ankylosing spondylitis (AS), axial spondyloarthritis (AxSpA), classification, concept, non-radiographic axial spondyloarthritis, pathophysiology, therapeutic strategies.

BACKGROUND AND OBJECTIVE

Axial spondyloarthritis (AxSpA) is the prototype of a family of inter-related yet heterogeneous diseases sharing common clinical and genetic manifestations: the spondyloarthritides (SpAs). The condition mainly affects the sacroiliac joints and axial skeleton, beginning with insidious-onset inflammatory back pain (IBP). It may also extend to peripheral joints with a pattern of asymmetrical arthritis, predominantly of the lower limbs, and with the frequent presence of enthesitis and dactylitis, and can also be associated with extra-articular manifestations such as uveitis, psoriasis, and inflammatory bowel disease, as well as displaying an association with the human leukocyte antigen B27 (HLA-B27).[1] The prevalence of AxSpA in Western populations is around 0.5%.[2] AxSpA is considered to be a prototype because it has a clear classification scheme, wider epidemiological data, and distinct therapeutic guidelines. However, the concept has not been immutable over time and has evolved tremendously at many levels over the past decades. The objective of this review is to describe the evolution of the AxSpA concept at the levels of classification and therapeutic strategy.

METHODS

A search of the US National Library of Medicine (PubMed) database was performed using the terms "axial spondyloarthritis", "spondylitis, ankylosing" AND "concept", with no limits on the date of publication. The search retrieved 166 articles, 33 of which were retained for the analysis according to the following inclusion criteria: pertinence to the review subject, relationship with AxSpA as a concept, relationship with the classification of AxSpA, relationship with the evolution of the treatment of AxSpA, and French or English language. The studies were divided into two categories: classification and treatment. A descriptive analysis of the evolution of these two concepts over time was performed.

CLASSIFICATION OF AXIAL SPONDYLOARTHRITIS

The term ankylosing spondylitis (AS) derives from the Greek words ankylosis (bent or crooked) and spondylos (vertebra),[3] and was previously known as Bechterew's disease (1892) and Marie—Strümpell disease (1884-1898).[4] The Egyptian pharaoh Ramses II and some of his descendants were thought to have AS, but this diagnosis was recently ruled out according to findings from computed tomography scans from mummies, with the diagnosis readjusted to diffuse idiopathic skeletal hyperostosis.[5] The first comparatively recent classification was published as the Rome criteria in 1961 and was based on clinical manifestations and sacroiliac plain X-rays, followed by the New York criteria in 1966, which introduced the radiographic grading of the sacroiliac joints. In 1984, the modified New York criteria for AS were published,[6] which introduced the concept of IBP. AS was diagnosed if a mandatory sacroiliitis was found on plain X-rays in addition to the presence of one clinical criterion (either chronic inflammatory low back pain and stiffness, limitation of motion of the lumbar spine, or limitation of chest expansion). Two subsequent European classifications were published in 1990 and 1991, the Amor criteria[7] and the European Spondyloarthropathy Study Group (ESSG) criteria,[8] respectively, but they addressed the SpA as a whole family of diseases, including the undifferentiated form of SpA, rather than the axial form specifically.

Due to the lack of pathognomonic clinical features or laboratory tests, the intermittent nature of the disease, and the wide availability of effective, over-the-counter symptomatic agents (nonsteroidal anti-inflammatory drugs [NSAIDs]), early diagnosis is difficult and the delay between symptom onset and diagnosis by X-rays according to the new criteria is very important, and can be up to 9 years.[9] A new classification system was necessary in order to help earlier identification of the disease. Furthermore, the introduction and standardisation of sacroiliac magnetic resonance imaging (MRI) revolutionised diagnosis of the disease, allowing earlier and more accurate identification of cases.[10] In addition, effective new therapies were available and this increased the importance of an earlier diagnosis. Therefore, the Assessment of SpondyloArthritis international Society (ASAS) published the ASAS classification predominantly for AxSpA in 2009,[11] with the term AxSpA being introduced for the first time (Figure 1).

AxSpA is an umbrella term that encompasses two entities: the first is the well-known AS, in which sacroiliitis is found on plain X-rays according to the modified New York criteria, and it is synonymous with radiographic AxSpA; the second is non-radiographic AxSpA, in which the diagnosis is based on sacroiliitis identified on MRI plus one clinical criterion, or based on a genetic criterion (HLA-B27) plus two clinical criteria (Table 1). The new criteria performed well in a validation study and demonstrated a sensitivity of 82.9% and a specificity of 84.4%, which outperformed the ESSG and Amor criteria even after incorporating 'sacroiliitis on MRI' into the earlier criteria.[12] Although the main advantage of the ASAS criteria remains a high sensitivity and an earlier diagnosis leading to an earlier treatment, a major drawback remains the poor sensitivity of the clinical arm, especially in populations with a high prevalence of HLA-B27, in which fibromyalgia cases may be wrongly classified as AxSpA.

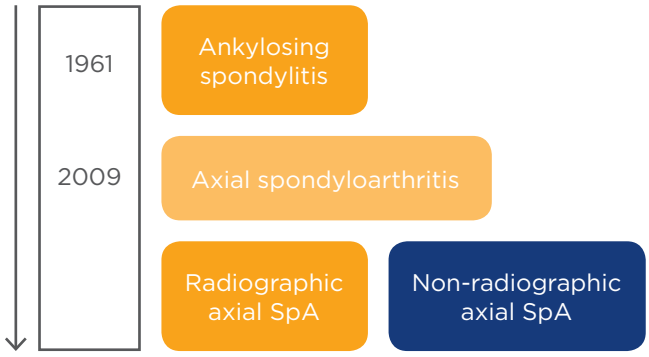

Figure 1: Evolution of the nomenclature of axial SpA.
SpA: spondyloarthritides.

Table 1: Comparison of the two main classification systems for axial spondyloarthritis.

	New York classification (1984)	ASAS classification (2009)
Clinical criteria	At least one of: • Chronic inflammatory low back pain and stiffness • Limitation of motion of the lumbar spine • Limitation of chest expansion	Mandatory: • Chronic back pain and age of onset <45 years Other SpA features: inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn's disease/ulcerative colitis, good response to NSAIDs, family history of SpA, HLA-B27, elevated CRP
Radiological criteria	Mandatory: • Sacroiliitis on plain X-rays (Grade 2 bilaterally or Grade 3-4 unilaterally)	Sacroiliitis on MRI (ASAS criteria) or on plain X-rays (New York criteria) + one other SpA feature
Genetic criteria	-	HLA-B27 + two other SpA features

ASAS: Assessment of SpondyloArthritis international Society; SpA: spondyloarthritides; HLA-B27: human leukocyte antigen B27; NSAID: nonsteroidal anti-inflammatory drug; CRP: C-reactive protein; MRI: magnetic resonance imaging.

Since the introduction of the terms 'radiographic' and 'non-radiographic' AxSpA, studies and discussions have tried to understand if these diseases have the same genetic, clinical, biological, and prognostic characteristics. These discussions have scientific implications but also regulatory consequences. The two entities share some similar characteristics, such as disease activity and treatment response rates, with a higher response in subgroups with higher objective signs of inflammation. Non-radiographic AxSpA is characterised by a higher prevalence of females and a lower level of C-reactive protein (CRP), reflecting a milder disease.[13] About 12% of the patients with non-radiographic AxSpA progress to AS over a period of 2 years, with elevated CRP and active sacroiliitis on MRI being the strongest predictors for such a progression. The current data consider the two entities to be part of a spectrum of the same disease.

THERAPY OF AXIAL SPONDYLOARTHRITIS

The 'window of opportunity' concept, which is very well established in rheumatoid arthritis (RA), is now under evaluation for AxSpA.[14,15] In theory, early diagnosis, treatment, and control of inflammation would prevent tremendous symptomatic burden and loss of function during the productive years of life. When looking at the evidence, MRI data support the window of opportunity concept: during tumour necrosis factor (TNF) antagonist therapy, pure inflammatory lesions resolved and no syndesmophytes developed at the same site, whereas complex MRI lesions combining inflammation and fatty infiltration were followed by same-site ossification.[16,17] Recent-onset symptoms and pure inflammatory MRI lesions, without fatty lesion depositions, seem to be associated with a better outcome.[14]

Another concept 'borrowed' from RA is the 'treat to target' (T2T) concept. However, unlike the well-established T2T guidance in RA, where clear outcome measures are standardised, the T2T concept for treating SpA is still immature. Clinical evidence of T2T in SpA is still lacking, and practical easy-to-measure outcomes are needed.[18] The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is currently used for therapeutic decision-making, with a cut-off score >4 indicating when to start TNF antagonist therapy; however, AS Disease Activity Score (ASDAS) values, incorporating CRP, have a significant influence on radiographic progression in AS and may currently be the best candidate for treatment decisions, as shown recently in the Outcome in Ankylosing Spondylitis International Study (OASIS)

cohort, where ASDAS correlated significantly with radiographic progression.[19]

The latest update to clinical management was published in 2011 by the ASAS group.[20,21] The cornerstones of treatment were education and physical exercise for non-pharmacological treatment, NSAIDs as first-line treatment, and TNF inhibitor therapy for pharmacological treatment. Data about the positive structural effect of continuous NSAIDs were considered a breakthrough in disease management since it was the first time that treatment reduced radiographic progression.[22] Later studies confirmed this protective effect and found that patients with a high risk of radiographic progression (elevated CRP, existing syndesmophytes) benefitted more from continuous NSAID treatment.[23,24]

Five TNF antagonists are now approved for patients with active AS: adalimumab, certolizumab, etanercept, golimumab, and infliximab. Recently, TNF antagonist biosimilars are also being approved for AS.[25] There is evidence that these agents reduce the clinical signs and symptoms of most patients with AxSpA, and they also reduce serum CRP levels and axial inflammation as detected by MRI.[25] In their first cornerstone studies, TNF antagonist therapies failed to prove a structural protective effect.[26,27] However, some recent studies suggested a structural protective effect with very long-term continuous use.[28,29] Further research is needed in order to confirm this structural effect, but it would face enormous methodological challenges. Similar responses to TNF antagonist therapies were found in AS and non-radiographic AxSpA.[30,31]

Diseases refractory to NSAIDs and TNF antagonists represent a challenge today. Other biological treatments used in RA, such as anakinra, rituximab, abatacept, and tocilizumab, have generated conflicting data and failed to earn their place in the therapeutic arsenal.[25] Promising biological agents efficacious in psoriatic arthritis are under investigation in AxSpA: ustekinumab, a fully humanised immunoglobulin G1k monoclonal antibody against the common subunit p40 of interleukin (IL)-12 and IL-23,[32] and secukinumab, a fully humanised monoclonal anti-IL-17A antibody.[33] Small molecules, such as inhibitors of phosphodiesterase 4 and Janus kinase inhibitors, may also be efficacious.[25]

CONCLUSION

The concept of AxSpA is a work in progress. The new ASAS classifications are a major advance for earlier diagnosis, but should be used carefully in order to avoid overdiagnosis by erroneously including patients with mechanical back pain or fibromyalgia. At the therapeutic level, many promising molecules are under investigation and should be available in the near future. However, therapeutic strategies need to be further investigated and more evidence supporting the window of opportunity concept are needed.

REFERENCES

1. Sieper J et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis. 2009;68 Suppl 2:ii1-i44.

2. Rudwaleit M, Taylor WJ. Classification criteria for psoriatic arthritis and ankylosing spondylitis/axial spondyloarthritis. Best Pract Res Clin Rheumatol. 2010;24:589-604.

3. Garg N et al. The concept of spondyloarthritis: where are we now? Best Pract Res Clin Rheumatol. 2014;28: 663-72.

4. ZORAB PA. The historical and prehistorical background of ankylosing spondylitis. Proc R Soc Med. 1961;54: 415-20.

5. Saleem SN, Hawass Z. Ankylosing spondylitis or diffuse idiopathic skeletal hyperostosis in royal Egyptian mummies of 18th-20th dynasties? CT and archaeology studies. Arthritis Rheumatol. 2014;66:3311-6.

6. van der Linden S et al. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27:361-8.

7. Amor B et al. [Criteria of the classification of spondylarthropathies]. Rev Rhum Mal Osteoartic. 1990;57:85-9.

8. Dougados M et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum. 1991;34:1218-27.

9. Feldtkeller E et al. Scientific contributions of ankylosing spondylitis patient advocacy groups. Curr Opin Rheumatol. 2000;12:239-47.

10. Baraliakos X. The contribution of imaging in the diagnosis and treatment of axial spondyloarthritis. Eur J Clin Invest. 2015;45:81-6.

11. Rudwaleit M et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68:777-83.

12. Rudwaleit M. New approaches to diagnosis and classification of axial and peripheral spondyloarthritis. Curr Opin Rheumatol. 2010;22:375-80.

13. Poddubnyy D, Sieper J. Similarities and differences between nonradiographic and radiographic axial spondyloarthritis: a clinical, epidemiological and therapeutic assessment. Curr Opin Rheumatol. 2014;26:377-83.

14. Claudepierre P. Spondyloarthritis: a window of opportunity? Joint Bone

Spine. 2014;81:197-9.

15. Robinson PC, Brown MA. The window of opportunity: a relevant concept for axial spondyloarthritis. Arthritis Res Ther. 2014;16:109.

16. Maksymowych WP et al. Suppression of inflammation and effects on new bone formation in ankylosing spondylitis: evidence for a window of opportunity in disease modification. Ann Rheum Dis. 2013;72:23-8.

17. Baraliakos X et al. Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with anti-TNF agents? A long-term observational study using MRI and conventional radiography. Ann Rheum Dis. 2014;73:1819-25.

18. Wei JC-C. Treat-to-target in spondyloarthritis: implications for clinical trial designs. Drugs. 2014;74:1091-6.

19. Ramiro S et al. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. Ann Rheum Dis. 2014;73:1455-61.

20. Braun J et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2011;70:896-904.

21. van der Heijde D et al. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. Ann Rheum Dis. 2011;70:905-8.

22. Wanders A et al. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. Arthritis Rheum. 2005;52:1756-65.

23. Poddubnyy D et al. Effect of non-steroidal anti-inflammatory drugs on radiographic spinal progression in patients with axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. Ann Rheum Dis. 2012;71:1616-22.

24. Kroon F et al. Continuous NSAID use reverts the effects of inflammation on radiographic progression in patients with ankylosing spondylitis. Ann Rheum Dis. 2012;71:1623-9.

25. Braun J et al. Emerging drugs for the treatment of axial and peripheral spondyloarthritis. Expert Opin Emerg Drugs. 2015;20:1-14.

26. van Der Heijde D et al. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. Arthritis Rheum. 2008;58:3063-70.

27. van der Heijde D et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. Arthritis Res Ther. 2009;11:R127.

28. Baraliakos X et al. Continuous long-term anti-TNF therapy does not lead to an increase in the rate of new bone formation over 8 years in patients with ankylosing spondylitis. Ann Rheum Dis. 2014;73:710-5.

29. Haroon N et al. The impact of tumor necrosis factor α inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum. 2013;65: 2645-54.

30. Sieper J et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). Ann Rheum Dis. 2013;815-22.

31. Song I-H et al. Similar response rates in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis after 1 year of treatment with etanercept: results from the ESTHER trial. Ann Rheum Dis. 2013;72:823-5.

32. Poddubnyy D et al. Ustekinumab for the treatment of patients with active ankylosing spondylitis: results of a 28-week, prospective, open-label, proof-of-concept study (TOPAS). Ann Rheum Dis. 2014;73:817-23.

33. Baeten D et al. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. Lancet. 2013;382:1705-13.

A UK BEST PRACTICE MODEL FOR DIAGNOSIS AND TREATMENT OF AXIAL SPONDYLOARTHRITIS

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ABSTRACT

Objectives: To examine the combined effectiveness of a care pathway for patients with suspected inflammatory back pain (IBP) in conjunction with an educational campaign targeting primary and secondary care and the local community.

Methods: Between June 2010 and June 2013, general practitioners referred patients fulfilling the Berlin IBP criteria into our Early Inflammatory Back Pain Service (EIBPS). Investigations were undertaken in line with our service model pathway and consultant rheumatologists made a diagnosis based on the Assessment of SpondyloArthritis international Society criteria. A concurrent educational awareness campaign addressing IBP and axial spondyloarthritis (AxSpA), aimed at primary and secondary care colleagues and the local community, was undertaken in order to assist early identification of IBP.

Results: Of the 222 patients referred into the EIBPS, 57 (26%) were newly diagnosed with AxSpA. A diagnosis of AxSpA was made in 48% of the patients with IBP or >1 SpA feature. The median time between onset of back pain and diagnosis was 3.1 years (mean: 5.7 years). Treatment with nonsteroidal anti-inflammatory drugs was initiated or continued as appropriate in 68/71 patients (96%; new and previously diagnosed AxSpA patients). All patients (100%) meeting the National Institute for Health and Care Excellence criteria for tumour necrosis factor inhibitor therapy were offered treatment, with 14 patients (45%) starting this treatment within 6 months of their initial EIBPS appointment.

Conclusion: Our EIBPS provides a best practice model for assessment and management of patients with suspected IBP in the UK. The pathway facilitates prompt admission of appropriate patients into the service and assists early diagnosis and management of AxSpA patients.

Keywords: Ankylosing spondylitis (AS), axial spondyloarthritis (AxSpA), best practice, diagnosis, diagnosis delay, low back pain, treatment.

INTRODUCTION

Axial spondyloarthritis (AxSpA) is an uncommon inflammatory disease that predominantly affects the spine and sacroiliac joints (SIJs) in young adults. It is therefore a rare cause of a frequent complaint and accounts for fewer than 5% of the patients who attend primary care with chronic back pain each year.[1] Early identification of this cohort has traditionally proven problematic in the UK, with an average interval between symptom onset and diagnosis of up to 10 years.[2] With the recent availability of highly effective therapies that work best in early active disease, there is an urgent need to address this delay.[3,4]

Non-radiographic AxSpA (nr-AxSpA) and radiographic AxSpA are proposed to belong to the same disease continuum,[5] with magnetic resonance imaging (MRI) demonstrating active inflammation of the SIJs from an early stage and a proportion of patients developing definite radiographic AxSpA within 10 years of follow-up.[5] This disease process may be slowed using recent advances in treatment, especially of early disease,[6] and so this argues strongly for earlier diagnosis and intervention that is universal. There is a wide variability in the ankylosing spondylitis (AS) facilities available in the UK and the majority of rheumatology services do not provide a dedicated early AS clinic.[2] The launch of 'Looking Ahead:

Best practice for the care of people with AS' in July 2010[7] offered solutions and suggested the use of a standardised service as a benchmark against which any department should be judged. This working group identified that "early recognition of the key features of AS" is essential for effective treatment. Chief among these key features is the identification of inflammatory back pain (IBP) in primary care settings. Recommendations included the training of professionals involved with spinal pain triage of inflammatory as well as mechanical spinal disorders, and that all patients identified should be evaluated for anti-tumour necrosis factor (TNF) therapy by a multidisciplinary team that includes a specialist physiotherapist. Even against a background of financial uncertainty, the majority of the obstacles identified here can be overcome with a named lead clinician holding a declared interest in AS and a specialist physiotherapist. This, along with a structured interface with primary care to target potential IBP patients early, would offer a model of best practice.

With the advent of newer therapies, the problem of delayed diagnosis acts as the obstacle to early effective treatment. It is also a significant barrier to job prospects for young adults during the critical years of their careers.[8] AS has been diagnosed traditionally using the modified New York criteria,[9] which require the presence of radiographic sacroiliitis, and these largely ignore early disease. Newer assessment models, such as the recent Assessment of SpondyloArthritis international Society (ASAS) criteria,[10] use MRI to identify early inflammatory change in SIJs and these should be standardised for early back-pain assessment clinics.

In the UK population, the mean delay in diagnosis has recently been established as 8.57 years.[2] By definition, therefore, this accepts ongoing symptoms over a number of years, irreversible loss of spinal mobility, function,[11] and persistent work incapacity[8] in a young population. Early treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) may slow bony progression,[12] and, more importantly, recent data show that patients with shorter disease duration demonstrate significantly reduced disease progression with anti-TNF therapy over 4 years.[6] The anti-TNF response is better if symptom duration is <10 years.[6,13] Early diagnosis also offers timely provision of exercise information, education, and available support networks to empower patients to assist self-management, which can reduce disease activity and improve return-to-work prospects.[14]

Early Identification of AxSpA

An ideal model would achieve earlier targeted referral and diagnosis, with identification of likely IBP within primary care as the goal. A back-assessment pathway that acts to prompt identification of IBP with early access to a dedicated service is the way forward. Lack of awareness of AS and its clinical features in primary care, and among other healthcare professions, is a likely contributing factor to lengthy delays. Jois et al.[15] showed inconsistencies in the knowledge of early features and management of AS in primary care. IBP is the primary symptom of AxSpA, with around 75% of AS patients experiencing this.[16] Conversely, the probability of a patient having AxSpA if they do not have IBP is <2%.[17] Using IBP as a screen in primary care is a simple and useful tool to assist with identifying patients who benefit from early referral. Programmed education in primary care is necessary to improve early detection of AxSpA,[15] but application and uptake requires a dedicated team. Improving public awareness of AxSpA and IBP within general practitioner (GP) surgeries, gyms, and shopping centres may lead to patients with these symptoms seeking help earlier. Recent research in New Zealand has demonstrated that public awareness campaigning results in a significant increase in referrals to rheumatology and an increase in diagnosis of AxSpA.[18]

Objectives for a Best Practice Model

i) To propose a care pathway for patients with suspected IBP in primary and secondary care.

ii) To lead a programme of ongoing education that identifies early IBP in primary care and musculoskeletal services.

iii) To examine the combined effectiveness of new referral parameters, GP and other healthcare professional (HCP) campaigns, and a community-based 'Back on Track' awareness campaign used to identify IBP.

iv) To determine the effect of this on delayed diagnosis in a given service.

v) To promote awareness of the early features of IBP, supported by the National Ankylosing Spondylitis Society (NASS) and, in some cases, sponsored by industry.

METHODS

Recruitment

Between June 2010 and June 2013, GPs and local musculoskeletal community services in the London boroughs of Waltham Forest and Redbridge were contacted by letter and email and asked to refer patients into the Early Inflammatory Back Pain Service (EIBPS) if they had chronic back pain (>3 months) and fulfilled two of the following four Berlin IBP criteria:[19] i) morning stiffness >30 minutes; ii) improvement with exercise but not with rest; iii) awakening in the second half of the night because of back pain; iv) alternating buttock pain. A referral proforma pack and EIBPS posters outlining the features of IBP were sent out in addition to guidance on locating the service on 'Choose and Book' for referral.

Awareness Campaign

All GPs within the two London boroughs were invited to attend ongoing teaching meetings throughout the 3 years, which included education regarding IBP, AxSpA, and our EIBPS using case histories and referrals from their surgeries. Physiotherapists based at the local hospitals within both boroughs were invited to attend an annual, interactive half-day course run by the AS rheumatologists and specialist AS physiotherapist at Whipps Cross Hospital. Hospital doctors, consultants, and physiotherapists within the department received teaching regarding identifying patients with IBP and associated AxSpA features. A community 'Back on Track' campaign supported by the NASS was initiated within local gyms, hospitals, and shopping arcades, with newspaper press releases and the local radio stations used to raise awareness of IBP and provide an opportunity for people with back pain to discuss their symptoms with consultant AS rheumatologists and a specialist AS physiotherapist off-site at weekends.

EIBPS Service Model

A screening pathway was developed and endorsed by NASS as outlined (Figure 1). Patients were referred into the EIBPS with a proposed presentation of IBP and/or other features suggestive of AxSpA according to ASAS criteria.[10] New referrals were screened by the AS rheumatologists prior to the patient attending the EIBPS in order to exclude non-spinal pain patients inappropriately booked into the service via 'Choose and Book'. During the first assessment, a thorough medical history was taken with particular emphasis on IBP and other SpA features, including: current or previous history of psoriasis, enthesitis, uveitis, peripheral arthritis, dactylitis, inflammatory bowel disease (IBD), reactive arthritis, good response to NSAIDS (<48 hours), and family history. All patients were discussed with, or reviewed by, a rheumatologist in order to limit any potential bias. The diagnostic investigations included: X-rays of SIJs if patients fulfilled the Berlin IBP criteria or if the AS rheumatologist deemed it necessary based on other SpA features; MRI scans of the whole spine and SIJs were undertaken for all patients with a normal or equivocal (sacroiliitis <Grade 2) plain film. Laboratory tests consisted of: human leukocyte antigen (HLA)-B27, C-reactive protein, and erythrocyte sedimentation rate, in addition to full blood count, liver function tests, and urea and electrolytes.

A diagnosis of AS (radiographic AxSpA) was made according to the modified New York criteria.[9] A diagnosis of nr-AxSpA was made according to the ASAS criteria.[10] Data describing patient SpA features and the time taken between onset of first symptoms and diagnosis were entered into a database and analysed. All patients with a new diagnosis of radiographic AxSpA or nr-AxSpA were formally reviewed by the AS rheumatologist to discuss optimal management of their condition. They were invited to attend an educational and exercise course on AxSpA led by the specialist AS physiotherapist and attended by a consultant rheumatologist as a question-and-answer session for early AS and treatment options. Patients were routinely monitored biannually following their diagnosis. However, this was flexible depending upon anti-TNF therapy screening requirements and severity of symptoms. Patients who fulfilled NICE criteria for anti-TNF therapy with a diagnosis of radiographic sacroiliitis (AS), failure of two NSAIDs, and two Bath Ankylosing Spondylitis Disease Activity Index scores >4 were offered treatment.

One of each patient's twice-yearly appointments was within a designated AS clinic, run by the AS consultant and AS physiotherapist, for functional and symptom monitoring, advice, and medication review. Patients requiring onward referral to other multidisciplinary team specialties (e.g. ophthalmology, gastroenterology, orthopaedics, dermatology, occupational therapy, physiotherapy, hydrotherapy, orthotist, social services) were discussed and actioned. A telephone advice service was provided to all AxSpA patients in

order to assist with managing flares, and early review in clinic was arranged as necessary. Patients had the support of their local NASS group, which ran weekly exercise classes using the hospital's hydrotherapy pool and gym and taught by physiotherapists with a keen interest in AxSpA. The collected data were analysed and mean values calculated.

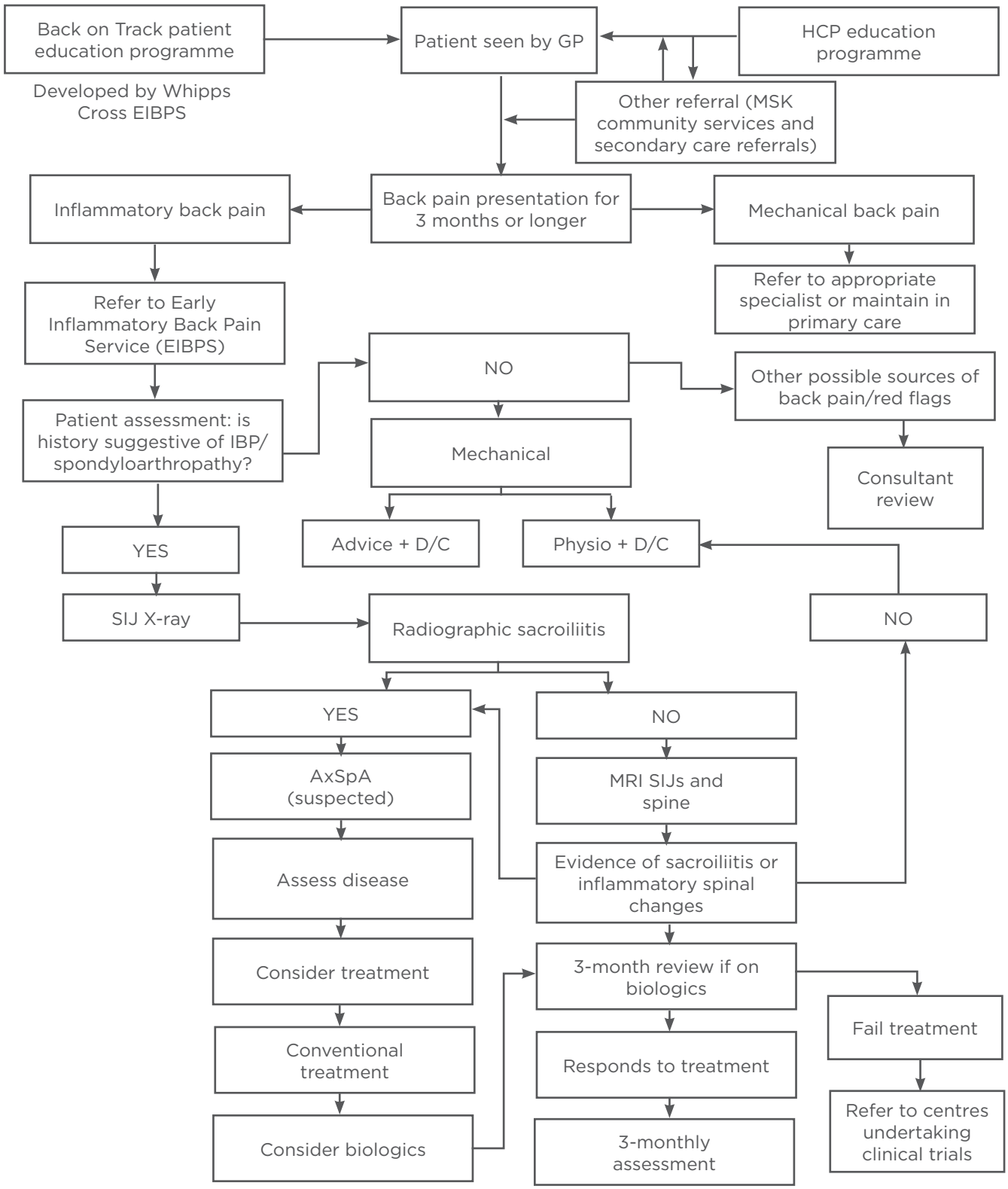

Figure 1: Early Inflammatory Back Pain Service (EIBPS) model.
GP: general practitioner; HCP: healthcare professional; MSK: musculoskeletal; EIBPS: Early Inflammatory Back Pain Service; IBP: inflammatory back pain; AS: ankylosing spondylitis; AxSpA: axial spondyloarthritis; MRI: magnetic resonance imaging; SIJ: sacroiliac joint.

RESULTS

Referral Guidelines

Between June 2010 and June 2013, a total of 222 patients were referred into the EIBPS by primary care doctors (n=207), extended-scope practitioners (physiotherapists) (n=3), and orthopaedists (n=12). Three patients were lost to follow-up and therefore excluded from the analysis.

Patient Characteristics

The mean age of all patients referred was 34 years (range: 16-64) and 50% were male (Table 1). Of the patients screened by the EIBPS, 64% had IBP and 48% of the patients presenting with IBP or >1 SpA feature (iritis, psoriasis, IBD, peripheral arthritis, dactylitis, family history of SpA) had a diagnosis of AxSpA.

Screening

The mean waiting time for a first new appointment with the EIBPS was 16 days, with 82% of patients seen within 3 weeks. In total, 142 patients (64%) fulfilled the Berlin IBP criteria. Mechanical back pain (MBP) was present in 80 patients (36%). A total of 149 patients (67%) were referred for an X-ray of their SIJs: 142 patients with IBP (100%) and 7 patients with MBP (3%) who did not fulfil the Berlin IBP criteria but had other features suggestive of spondyloarthropathy. Fourteen of these patients (9%) had a pre-existing diagnosis of AS (radiographic AxSpA) confirmed on plain films. A total of 41 of the 149 referred patients (28%) were given a new diagnosis of radiographic AxSpA following their X-ray. A total of 93 patients with normal or equivocal X-ray findings were referred for an MRI scan of the whole spine and SIJs in order to investigate further. Sixteen patients (17%) displayed findings suggestive of nr-AxSpA. A new diagnosis of AxSpA was made in 26% of all referred patients (Figure 2).

Diagnosis Delay

The median duration from the first onset of back pain to diagnosis of AxSpA was 3.1 years (range: 0.25-30; mean: 5.8 years), was 2.5 years (range: 0.25-20; mean: 5.3 years) for diagnosis of nr-AxSpA, and was 4.0 years (range: 0.25-30; mean: 6.0 years) for diagnosis of radiographic AxSpA.

Commencement of Treatment

At the time of diagnosis, 96% (n=68) of the AxSpA patients were taking NSAIDs. All patients (100%; n=37) that met NICE criteria for anti-TNF therapy were offered treatment, with 84% (n=31) passing screening and 45% (n=14) starting treatment within 6 months of their first appointment with the EIBPS. Treatment onset was delayed in the remaining 17 patients due to positive tuberculosis screening results requiring prophylactic treatment, and due to patient delays over discussion and consent.

Cost Analysis

The added cost of the service to our practice was a funded, 0.5 part-time senior physiotherapist (£18,000 per annum) who was trained by attending consultant-led AS clinics and then mentored in establishing early AS clinics for 6-9 months. Patients were gradually transferred from other general clinics to the specialist by generating a referral pathway for primary care, and this had no additional cost burden.

Table 1: Referred patient characteristics.

Patient group	Mean age (range), years	Males, %
All patients (n=222)	34 (16-64)	49.5
All IBP patients (n=142)	33 (16-61)	57.7
Existing radiographic AxSpA patients (n=15)	37 (23-50)	71.4
New diagnosis nr-AxSpA (n=16)	28.5 (16-42)	62.5
New diagnosis radiographic AxSpA (n=41)	35 (17-61)	70.0
New diagnosis peripheral SpA (n=5)	33.8 (29-40)	80.0
Lost to follow-up (n=3)	34.3 (29-43)	0

IBP: inflammatory back pain; AxSpA: axial spondyloarthritis; nr-AxSpA: non-radiographic axial spondyloarthritis; SpA: spondyloarthritis.

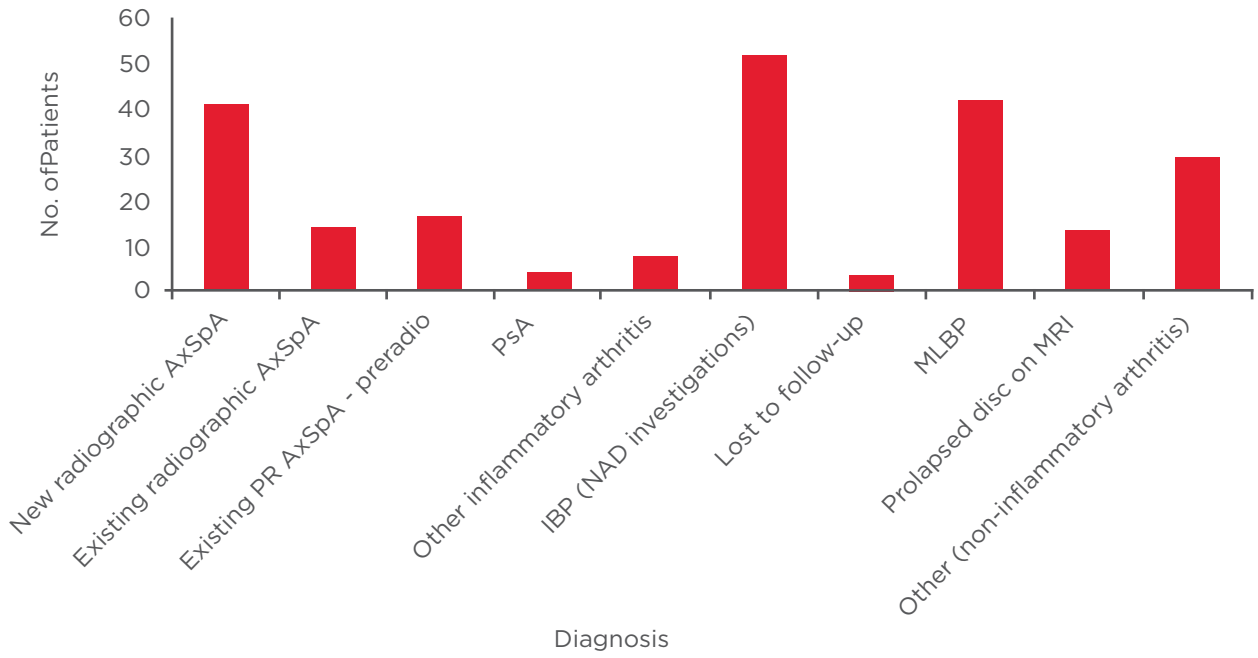

Figure 2: Diagnosis of all patients referred into the EIBPS (n=222).
IBP: inflammatory back pain; AxSpA: axial spondyloarthritis; PsA: psoriatic arthritis; EIBPS: Early Inflammatory Back Pain Service; MRI: magnetic resonance imaging; MLBP: mechanical low back pain.

DISCUSSION

The Whipps Cross' EIBPS provides an efficient and feasible best practice model based on the NASS 'Looking Ahead' recommendations for diagnosing and managing AxSpA. Almost two-thirds (64%) of patients referred into the service fulfilled the Berlin criteria for IBP. Further investigations revealed that almost half of these patients (48%) fulfilled the ASAS criteria for a diagnosis of nr-AxSpA or radiographic AxSpA. The overall service yield for diagnosing AxSpA from the applied referral parameters, combined awareness campaigns, and primary care education is high (38%), with an additional 9% having confirmation of a pre-existing diagnosis of radiographic AxSpA. Several recent studies have investigated referral strategies in different countries,[20-23] as delayed diagnosis results from difficulty in identifying IBP.[20] The diagnostic yield for AxSpA is higher when referral parameters, such as imaging and HLA-B27, are included over clinical features alone (41.8% versus 36.8%).[20] However, the authors note that including investigations within referral guidelines may result in inappropriate tests and imaging in primary care. Differentiating IBP from MBP in a busy GP clinic with simple questions provides a valuable screen for SpA and onward referral to specialist care.

Our EIBPS demonstrated a low median delay in diagnosis of 3.1 years. Mean diagnosis delay (5.8 years) was reduced significantly over routine UK rheumatology departments.[11] Brandt and colleagues[24] also demonstrated a shortened mean symptom duration of 7.7 years from initial onset to diagnosis when applying referral parameters in orthopaedics and primary care. We are unable to say whether the addition of a GP education and community awareness campaign assisted earlier diagnosis, but we are unaware of another UK study with a median delayed diagnosis below 5 years. The recent use of ASAS criteria that combine clinical, laboratory, and imaging parameters to diagnose patients early may influence the reduction in delay that we report. Despite the significant improvement observed in our cohort, a median gap of 3.1 years (mean: 5.8 years) for formal diagnosis is still disappointing, with a majority of patients still diagnosed with irreversible radiographic damage. It is reasonable to hypothesise that the next few years may yield greater reductions in diagnosis delay as the effects of the IBP awareness campaign filter through the system. Nevertheless, the efforts to promote awareness of AxSpA to frontline HCPs and secondary care should continue. A limitation of this study is that subjective questioning to identify IBP was collected within routine appointments by a specialist physiotherapist and not necessarily

using a standardised questionnaire. The authors attempted to limit bias by using a single, trained physiotherapist for all assessments.

Ensuring patients with AxSpA are managed within specialist services in rheumatology and have access to an expert multidisciplinary team with experience in inflammatory arthritis is a key recommendation in the 'Looking Ahead' publication.[7] The EIBPS provides regular disease monitoring of patients by a consultant rheumatologist and specialist AS physiotherapist and opportunities for patients to attend an educational and exercise group course, as well as ongoing weekly exercise and hydrotherapy sessions run by the NASS and Trust physiotherapists.

The EIBPS demonstrates that prompt access to drug treatments, such as NSAIDs and anti-TNF therapy, is possible. In our cohort, 96% of the AxSpA patients were taking NSAIDs at diagnosis. Supportive evidence showing that NSAIDs may slow the progression of spinal bony changes in AS now exists,[5,12,25] especially in patients with elevated acute-phase reactants, and, as such, a risk/benefit analysis should be performed for each individual patient. Furthermore, anti-TNF therapy has consistently demonstrated symptom control, with work and lifestyle benefits in patients with radiographic AxSpA.[26,27] All patients should be evaluated for anti-TNF therapy as recommended by the NASS 'Looking Ahead' initiative, and as demonstrated within our service. Timely commencement of biological agents is essential in those patients fulfilling the NICE criteria. Almost half of our patients started anti-TNF therapy within 6 months of their first consultation with the EIBPS.

The EIBPS model provides a cost-efficient and replicable service for patients with suspected IBP, and diverts patients out of general rheumatology clinics and into a specialist service providing prompt and accurate diagnosis and management. There was a significant reduction in diagnostic delay in our cohort and the added costs we demonstrate for such a service should not deter commissioners or trust boards. We recommend that all trusts consider this best practice model in conjunction with primary care education within the local catchment area in order to raise the profile of IBP.

KEY MESSAGES

i) Delay in the diagnosis and management of AxSpA continues to be a major issue in the UK.

ii) IBP service pathways, supported in the NASS 'Looking Ahead' recommendations, facilitate the early diagnosis and management of AxSpA and shorten diagnostic delay.

iii) Our best practice model provides a feasible, cost-effective pathway for the development of other EIBP services.

REFERENCES

1. McKenna R. Spondyloarthritis. Reports on the Rheumatic Diseases. 2010;6(5):1-6.

2. Hamilton L et al. Services for people with ankylosing spondylitis in the UK--a survey of rheumatologists and patients. Rheumatology (Oxford). 2011;50(11): 1991-8.

3. Weiß A et al. Good correlation between changes in objective and subjective signs of inflammation in patients with short- but not long duration of axial spondyloarthritis treated with tumor necrosis factor-blockers. Arthritis Res Ther. 2014;16:R35.

4. Glintborg B et al. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. Ann Rheum Dis. 2010;69(11):2002-8.

5. Poddubnyy D et al. Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. Arthritis Rheum. 2012;64(5):1388-98.

6. Haroon N et al. The impact of tumour necrosis factor inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum. 2013;65(10):2645-54.

7. National Ankylosing Spondylitis Society. Looking Ahead: Best practice for the care of people with ankylosing spondylitis. 2010. Available at: http://www.nass.co.uk/campaigning/looking-ahead/. Last accessed: 23 May 2014.

8. Healey EL et al. Impact of ankylosing spondylitis on work in patients across the UK. Scand J Rheumatol. 2011;40(1):34-40.

9. van der Linden S et al. Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria. Arthritis Rheum. 1984;27:361-8.

10. Rudwaleit M et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part 1): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis. 2009;68(6):770-6.

11. Landewé R et al. Physical function in ankylosing spondylitis is independently determined by both disease activity and radiographic damage of the spine. Ann Rheum Dis. 2009;68:863-7.

12. Wanders A et al. Nonsteroidal anti-inflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomised clinical trial. Arthritis Rheum. 2005;52(6):1756-65.

13. Rudwaleit M et al. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor blockers in ankylosing spondylitis. Ann Rheum Dis. 2004;63(6):665-70.

14. Ehlebracht-König I, Bönisch A. [Patient education in the early treatment

of ankylosing spondylitis and related forms of spondyloarthritis]. Wien Med Wochenschr. 2008;158(7-8):213-7.

15. Jois R et al. Recognition of inflammatory back pain and ankylosing spondylitis in primary care. Rheumatology. 2008;47(9):1364-6.

16. Gran JT. An epidemiological survey of the signs and symptoms of ankylosing spondylitis. Clin Rheumatol. 1985;4(2): 161-9.

17. Rudwaleit M et al. How to diagnose axial spondyloarthritis early. Ann Rheum Dis. 2004;63(5):535-43.

18. Harrison AA et al. Comparison of rates of referral and diagnosis of axial spondyloarthritis before and after an ankylosing spondylitis public awareness campaign. Clin Rheumatol. 2014;33(7):963-8.

19. Rudwaleit M et al. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. Arthritis Rheum. 2006;54(2):569-78.

20. Poddubnyy D et al. Evaluation of 2 screening strategies for early identification of patients with axial spondyloarthritis in primary care. J Rheumatol. 2011;38(11):2452-60.

21. Braun A et al. Identifying patients with axial spondyloarthritis in primary care: how useful are items indicative of inflammatory back pain? Ann Rheum Dis. 2011;70(10):1782-7.

22. Sieper J et al. Comparison of two referral strategies for diagnosis of axial spondyloarthritis: the Recognising and Diagnosing Ankylosing Spondylitis Reliably (RADAR) study. Ann Rheum Dis. 2013;72(10):1621-7.

23. Hermann J et al. Early spondyloarthritis: usefulness of clinical screening. Rheumatology (Oxford). 2009;48(7):812-6.

24. Brandt H et al. Performance of referral recommendations on patients with chronic back pain and suspected axial spondyloarthritis. Ann Rheum Dis. 2007;66(11):1479-84.

25. Kroon F et al. Continuous NSAID use reverts the effects of inflammation on radiographic progression in patients with ankylosing spondylitis. Ann Rheum Dis. 2012;71(10):1623-9.

26. Braun J et al. Persistent clinical response to the anti-TNF antibody infliximab in patients with ankylosing spondylitis over 3 years. Rheumatology. 2005;44(5):670-6.

27. Brandt J et al. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. Arthritis Rheum. 2003;48(6):1667-75.

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