Promising Results for TYK2 Inhibition in Lupus Erythematosus
In the phase 2 PAISLEY trial, patients with active systemic lupus erythematosus treated with deucravacitinib achieved SLE Responder Index 4 in 58.2% of the cases compared with 34.4% in placebo-treated patients.

Oral Treatment Beneficial for Juvenile Idiopathic Arthritis
Baricitinib demonstrated great potential for flare prevention in juvenile idiopathic arthritis in the phase 3 JUVE-BASIS trial. Disease exacerbation was noted in 17% of participants on active treatment compared with >50% in placebo-treated participants.

Sarilumab Successful for Polymyalgia Rheumatica
Nearly 30% of participants receiving sarilumab in the phase 3 SAPHYR study achieved sustained remission. Furthermore, participants on sarilumab had a significant reduction of flares compared with those receiving placebo.
Contents

Letter from the Editor

3 Late-Breaking Oral Abstracts
3 TYK2 inhibition: the future of treating lupus erythematosus?
3 Psoriatic arthritis: significant improvement with bimekizumab
4 Baricitinib could open the door to oral treatment for juvenile idiopathic arthritis
5 Sarilumab for polymyalgia rheumatica led to sustained remission and fewer flares

6 Spotlight on Rheumatoid Arthritis
6 Comorbid depression comes with a profoundly higher mortality risk in RA
6 Preventive treatment with methotrexate benefits pre-RA patients with arthropgia
7 Risk factors for dementia in RA patients discovered
8 VTE in global registry data more common in JAK inhibitor-treated RA patients

9 Spondyloarthropathies: Novel Developments
9 How to treat enthesitis in 2022
10 Baseline cardiovascular risk linked to higher rates of MACE in PsA and PsO patients receiving tofacitinib
11 Treat-to-target dose reduction effective in spondyloarthritis
12 A novel oral treatment possibility for non-radiographic axSpA on the horizon
13 Many RA and PsA patients have problems with their sex life

14 What Is Hot in Osteoarthritis?
14 New treatments in osteoarthritis
15 OA associated with alcohol and drug abuse
16 Body mass index increase associated with structural changes in knee OA

16 What Is New in Lupus and Scleroderma?
16 Inhibition of Bruton’s tyrosine kinase: a new way of approaching SLE?
17 Pregnancies in SLE: Many complications for mothers and their unborn children
18 Lupus nephritis: efficient treatment may reduce the risk of kidney disease advancement
18 Antifibrotic therapy with nintedanib is beneficial for patients with negative prognostic factors

19 Best of The Posters
19 Alarmingly low activity in patients with non-inflammatory and inflammatory rheumatic disease
20 High prevalence of fibromyalgia in patients with inflammatory bowel disease
Dear colleagues,

The EULAR 2022 Congress took place in Copenhagen, Denmark, between the 1st and 4th of June 2022 and was the first in-person EULAR gathering since 2019. The meeting was attended by 8,200 delegates with a further 6,200 online attendees. Attendees have long memories of the last EULAR in Denmark with sustained rainfall in 2009, but, on this occasion, they were surprised by the very pleasant weather during the event. Despite Denmark being one of the first countries to lift COVID-19 restrictions, attendees arriving at the congress centre had to produce proof of immunity to COVID-19 and to navigate airport-type security with glossy coated alsatians in reserve behind the barriers. Nevertheless, like salmon excitedly returning to the spawning grounds, the delegates patiently funnelled through all obstacles to the upstream pools of knowledge, camaraderie, and creativity - that collectively embody the unique experience of the EULAR annual congress.

As usual, the meeting had an excellent balance of clinical and translational Rheumatology and a not unexpected number of abstracts and talks related to the SARS-CoV-2 virus. Overall, Rheumatology patients have fared better than expected, given the concerns of drug- or disease-related immunosuppression just over 2 years ago. Herein we select a series of abstracts that capture current Rheumatology activity across disease areas, including the growing interest in inflammatory arthritis prevention and newer therapeutic avenues for JAK inhibitors. We also highlight some state-of-the-art talks across different areas to give delegates a bigger picture of where the field is moving. We are eagerly looking forward to the continuation of normal EULAR meeting activity in the coming years.

Sincerely,
Prof. Dennis McGonagle
Late-Breaking Oral Abstracts

TYK2 inhibition: the future of treating lupus erythematosus?

Active systemic lupus erythematosus (SLE) treated with deucravacitinib led to promising response rates measured as SLE Responder Index (SRI) 4. In the phase 2 PAISLEY trial, up to 58.2% of participants met the endpoint of SRI (4), significantly more than the 34.4% on placebo.

“TYK2 is a Janus kinase that only mediates signalling through the type-1 interferon, IL-12 and IL-23 receptors, and it is not involved in the signalling of other cytokine pathways. This is an attractive therapeutic target for lupus,” Prof. Eric Morand (Monash University, Australia) explained the rationale of the PAISLEY study (NCT03252587) [1]. This randomised-controlled, phase 2 trial evaluated TYK2 inhibition through deucravacitinib as a treatment for active SLE. The primary endpoint was the number of participants who met the response criteria for SRI (4) at week 32. All 363 participants were on stable background medication and lacked severe organ-threatening disease. They were randomised 1:1:1:1 to either deucravacitinib 3 mg twice daily, 6 mg twice daily, 12 mg once daily, or placebo. Between week 8 and week 20 of the trial, a tapering of corticosteroids to 7.5 mg/day was obligatory. Thereafter, corticosteroids were kept stable until week 32. “Following that, there was an optional steroid taper to week 40 and an 8-week period of stable steroids to week 48; at which time, multiple, multiplicity-adjusted key secondary outcomes were also measured,” Prof. Morand stated.

Participants were about 40 years old, predominantly women, and had a mean BMI of 26.8 kg/m². Most of them had extensive background therapy. Just over 80% were treated with corticosteroids, 49.9% of them at a ≥10 mg daily dosage, 51.8% took immunosuppressants, and 32.2% had a triple treatment that further included antimalarials.

The trial met its primary endpoint: SRI (4) response was significantly lower on placebo (34.4%) than in the deucravacitinib groups: 58.2% (3 mg twice daily; P=0.0006), 49.5% (6 mg twice daily; P=0.021), and 44.9% (12 mg once daily; P=0.0781). “All secondary outcome measures were achieved or meaningfully improved at week 48 including SRI (4), BICLA (British Isles Lupus Assessment Group-based Composite Lupus Assessment), low disease activity state, reduction in skin disease, and reduction in arthritis,” Prof. Morand highlighted. A reduction in anti-dsDNA antibody titer and an increase in C4 levels were also observed.

Concerning safety up to week 48, no deaths occurred, nor did any major adverse cardiac or thrombotic events. Serious adverse events were observed in 12.2% of placebo recipients and between 7.7% and 8.6% in the different deucravacitinib groups. Prof. Morand underlined that there were no signals for either COVID-19 or herpes zoster. However, skin-related adverse events (the nature of which were not defined in the abstract) were higher in the deucravacitinib groups (16.5%, 34.4%, 33.7% vs 13.3% on placebo). Prof. Morand also pointed out that deucravacitinib did not affect haematologic markers or standard biochemistry. He concluded that “Deucravacitinib shows promise as a novel therapy for SLE and warrants further investigation in phase 3 trials.” It is also noted that the obligatory corticosteroid tapering strategy during the trial may be a novel way to evaluate promising new agents for SLE.

Psoriatic arthritis: significant improvement with bimekizumab

An ACR50 response was observed in over 40% of patients with psoriatic arthritis (PsA) treated with bimekizumab in the phase 3 BE OPTIMAL trial. The study drug demonstrated significant superiority in the primary and all ranked secondary endpoints.

“Bimekizumab is an antibody that blocks IL-17A and IL-17F; it is not bi-specific, there are not 2 different binding arms, it is 1 antibody that happens to bind an epitope that is shared between the 2 cytokines, and so this is actually a new molecular entity, a new combinatorial target,” Prof. Iain McInnes (Glasgow University, United Kingdom) said in his introduction [1]. He presented the late-breaking phase 3 results and the 24-week interim analysis of the BE OPTIMAL study (NCT03895203) assessing bimekizumab in biologics-naive patients with PsA.

The trial enrolled 852 adult patients with at least 3 tender and 3 swollen joints, and 1 active psoriatic lesion and/or documented history of psoriasis. As may be expected in a trial for PsA, the baseline features of the cohort included a mean age of around 49 years, over 50% women, and just under 60% on concomitant methotrexate. About 50% of the participants had skin involvement with a body surface area affected by psoriasis of ≥3%.

The 16-week, double-blind phase consisted of 3 study arms, in which participants were treated with placebo (n=281), bimekizumab 160 mg every 4 weeks (n=431), or adalimumab 40 mg every 2 weeks (n=140) in a reference arm. After week 16, an active treatment-blind period followed, in which placebo participants were switched to bimekizumab until week 52. Prof. McInnes underlined that the study was neither designed nor powered for a head-to-head comparison of bimekizumab and adalimumab. The primary endpoint was the ACR50 response at week 16.

The study was positive, with statistically significant more participants in the bimekizumab arm achieving ACR50 than placebo recipients at week 16: 43.9% versus 10.0% (OR 7.1; 95% CI 4.6–11.0; P<0.001). The respective findings for ACR20 and ACR70 were 62.2% versus 23.8% and 24.4% versus 4.3%. “Through week 24, those responses were maintained and consistent, and the placebo patients who crossed over to bimekizumab rapidly recovered rates of response to be broadly similar to those patients who had already achieved response by week 16,” Prof. McInnes further stated. The study also showed similar levels of ACR50 responses between the adalimumab reference arm and the bimekizumab arm.

As for the ranked secondary outcomes, Prof. McInnes highlighted that bimekizumab was significantly superior to placebo when it came to skin amelioration at week 16, with rates of 61.3% versus 2.9% (P<0.001) reaching a Psoriasis Area and Severity Index (PASI)90 and 47.5% versus 2.1% reaching PASI100 (nominal P<0.001). Bimekizumab also significantly outperformed placebo in the achievement of minimal disease activity and inhibition of structural progression.

The safety evaluation revealed no unexpected findings. “I want to point out fungal infections, which occurred more frequently in the recipients of bimekizumab than adalimumab,” Prof. McInnes added. Overall, bimekizumab was deemed well tolerated.


Baricitinib could open the door to oral treatment for juvenile idiopathic arthritis

In a phase 3 withdrawal trial, the JAK 1/2 inhibitor baricitinib demonstrated great potential for flare prevention in juvenile idiopathic arthritis (JIA). Disease exacerbation was noted in 17% of participants on the study drug but in more than half of the placebo-treated participants.

The term juvenile idiopathic arthritis subsumes various acquired immune-mediated diseases [1–3]. Currently, treatment options such as conventional synthetic or biologic disease-modifying antirheumatic drugs (csDMARD or bDMARD) are frequently used. “Our patients and parents have been waiting for oral alternatives to injectable drugs and the JAK inhibitors have come at the right time,” Prof. Athimalaipep Ramanan (Bristol Medical School, United Kingdom) expressed as he reported on the phase 3 JUVE-BASIS trial (NCT03773978) [1].

JUVE-BASIS assessed baricitinib in JIA with an unusual design. “All participants, in order to be ethical and to not subject our paediatric patients to placebo, were given access to the drug, and the responders were randomised at 12 weeks on a 1 to 1 basis to either continue the drug or switch to placebo,” Prof. Ramanan explained. The trial included participants with different forms of JIA such as enthesitis-related JIA, polyarticular JIA, and juvenile psoriatic arthritis. The double-blind withdrawal period extended from week 12 through 44 and the primary endpoint was the time to disease flare. Enrolled participants (n=220) had to be between 2 and 18 years old with a history of inadequate response to csDMARD or bDMARD.

At baseline, the mean age of the participants was 13.3 years, and the mean disease duration was 4 years. Of the 220 participants, 52.7% had previously been treated with biologics, 57.7% were on methotrexate, and 32.7% were on corticosteroids.

After the open-label lead-in 12-week period, JIA-ACR30 responses were reached by 76.3%, with corresponding rates for JIA-ACR50 at 63.5%, JIA-ACR70 at 46.1%, and JIA-ACR90 at 20.1%. “But the key was really in the withdrawal phase,” Prof. Ramanan stressed. Of the participants who stayed on baricitinib, 17.1% had a flare compared with 50.6% in the group that was switched to placebo (P<0.001; see Figure). “Not only do those who get switched to placebo...
have a higher incidence of flaring, but they were also more likely to flare quickly (as quickly as 4 weeks),” Prof. Ramanan commented on this significant result in the primary endpoint with a hazard ratio of 0.241 (P<0.001) in favour of baricitinib.

Figure: Baricitinib significantly increased the time to disease flare and decreased the frequency of disease flares versus placebo [1]

As safety might be even more important in paediatric patients than in adults, adverse events (AEs) were looked at in the lead-in period as well as the double-blind phase. In weeks 0–12, the discontinuation rate due to AEs was 0.9%. During the withdrawal part, 2 participants in the placebo and 1 participant in the baricitinib arm ended the trial because of AEs. During the withdrawal part, 2 participants in the placebo and 1 participant in the baricitinib arm ended the trial because of AEs. During the withdrawal part, 2 participants in the placebo and 1 participant in the baricitinib arm ended the trial because of AEs. During the withdrawal part, 2 participants in the placebo and 1 participant in the baricitinib arm ended the trial because of AEs. During the withdrawal part, 2 participants in the placebo and 1 participant in the baricitinib arm ended the trial because of AEs. During the withdrawal part, 2 participants in the placebo and 1 participant in the baricitinib arm ended the trial because of AEs. During the withdrawal part, 2 participants in the placebo and 1 participant in the baricitinib arm ended the trial because of AEs. During the withdrawal part, 2 participants in the placebo and 1 participant in the baricitinib arm ended the trial because of AEs. During the withdrawal part, 2 participants in the placebo and 1 participant in the baricitinib arm ended the trial because of AEs.

Serilumb for polymyalgia rheumatica led to sustained remission and fewer flares

Nearly 30% of participants receiving IL-6 inhibition in the randomised, phase 3 SAPHYR study achieved sustained remission. Furthermore, participants on sarilumab had a significant reduction of flares compared with those receiving placebo.

Elevated IL-6 levels in polymyalgia rheumatica (PMR) have been linked to relapse and increased need for corticosteroids [1–3]. This led to the exploration of IL-6 inhibition with sarilumab as a potential therapeutic agent [1]. The phase 3, randomised, double-blind SAPHYR trial (NCT03600818) included patients with PMR ≥50 years who had at least 1 flare within 12 weeks before the trial while being on ≥7.5 mg of prednisolone. The study aimed to enrol 280 patients, but recruitment halted at 118 participants due to the COVID-19 pandemic.

The participants were allocated to either placebo plus 52-week glucocorticoid taper or sarilumab 200 mg every 2 weeks plus a 14-week of glucocorticoid taper. The primary endpoint was defined as the rate of participants achieving sustained remission at week 52. This included disease remission at week 12 plus the absence of flares, CRP normalisation, and adherence to glucocorticoid taper from weeks 12–52.

The mean age of the participants was about 70 years, and they were mostly women. The median PMR duration was 292 days in the sarilumab arm and 310 days in the placebo arm. “The median number of previous flares per patient was 2 and that was similar between the 2 groups, and many of these patients had received prior immunosuppression,” Prof. Bhaskar Dasgupta (Anglia Ruskin University, United Kingdom) further specified.

At week 52, a statistically significant difference was seen between sarilumab and placebo with 28.3% versus 10.3% (P=0.0193) attaining sustained remission, respectively. Prof. Dasgupta further highlighted that all the components of
sustained remission showed a better result for the sarilumab arm compared with the control arm. The study drug also clearly delayed the time to the first flare, and the risk of having a flare on sarilumab versus placebo was determined with a hazard ratio of 0.56 (95% CI 0.35–0.90). In the light of the study protocol, the researcher expected a higher use of glucocorticoid in the placebo arm. "But we saw a 200 mg difference between the actual and the expected use in the placebo arm, which is related to a higher incidence of flares in the placebo arm," Prof. Dasgupta stated. The safety profile of sarilumab observed in SAPHYR was consistent with earlier findings.

"We were very excited to particularly concentrate on patient-reported outcomes because we know from our previous studies that patient-reported outcomes in terms of PMR quality-of-life are actually lower at onset than what we see with rheumatoid arthritis," Prof. Dasgupta mentioned. In the current trial, sarilumab demonstrated an overall positive influence on quality-of-life for patients with PMR.


Spotlight on Rheumatoid Arthritis

Comorbid depression comes with a profoundly higher mortality risk in RA

According to a large, Danish register analysis, the risk of mortality rises markedly for patients with rheumatoid arthritis (RA) who are also diagnosed with depression. In those younger than 55 years, the risk was increased more than 6 times.

A high prevalence of depressive disorders and links between depression and various long-term outcomes in RA have been observed [1]. "Although antidepressants are used for different indications, we have recently described that, in RA, the most frequent indication for filling antidepressants is depression," Dr Jens Kristian Pedersen (Odense University Hospital, Denmark) stated [2,3]. The presented cohort study investigated the mortality risk in patients with incident RA and depression [3]. Data was collected from various nationwide Danish registries. The presence of depression was defined as the first filling of an antidepressant prescription. The follow-up period for the all-cause mortality risk was from January 2008 to December 2018. Included in the analysis was data on 11,071 RA patients equalling 56,993 person-years of follow-up.

About 10% of the participants (n=1,095) had a filling of antidepressants during the follow-up period. The median age was 61 years, 66% were women, and 64% had seropositive RA. There was some variance between those with and without exposure to antidepressants. "In those exposed, the age distribution was different, the fraction of women was higher, a lower fraction had seropositive RA, and the median Health Assessment Questionnaire Disability Index (HAQ) and Disease Activity Score-28 (DAS28) were higher than in those not exposed," Dr Pedersen pointed out.

The results of the adjusted analysis for mortality hazard in RA patients with or without depression revealed the highest risk for exposed patients under the age of 55 years (HR 6.66; 95% CI 2.80–15.85). Corresponding HR for the other age groups receiving antidepressants were 3.3 for 55–70 years and 2.94 for >70 years old. Mortality was increased by depression in men (HR 3.70) and women (HR 2.91), as well as seropositive (HR 3.45) and seronegative RA (HR 3.08). "According to exposure status (to antidepressants), the cumulative mortality followed 2 clearly different paths: the mortality curves separated early and already within the first and second year of follow-up," Dr Pedersen commented on the Kaplan-Meier curves for exposed and non-exposed participants.


Preventive treatment with methotrexate benefits pre-RA patients with arthralgia

For the first time, a study demonstrated the benefit of arthralgia treatment with methotrexate before rheumatoid arthritis (RA) is diagnosed. Although the advancement to RA could only be delayed, the burden of disease was significantly reduced in this proof-of-concept study.
The window of opportunity for the treatment of RA is often seen in early disease, as there is ample evidence that effective disease modification with disability reduction or prevention is possible [1,2]. One question that has not been answered yet is whether RA can be prevented in patients with arthralgia who are at risk for RA. "So far, 2 trials have been performed in this phase, but these found no prevention of RA." This could depend on the chosen treatments or selected outcomes," stated Dr Doortje Krijbolder (Leiden University Medical Centre, the Netherlands) [1]. The randomised, 2-year proof-of-concept TREAT EARLIER study tested methotrexate versus placebo for reduction of RA development and burden of disease in patients with arthralgia. Included were 236 participants with a clinically suspect arthralgia plus subclinical MRI-detected joint inflammation of the hand or foot. They were treated either with 1 sole injection of 120 mg methylprednisolone and subsequent methotrexate (up to 25 mg/week) over 1 year or a placebo substitute. The baseline characteristics showed a mean age of 46.5 years, over 60% were women, and ≥20% were positive for anti-citrullinated protein antibodies (ACPA). As for the development of persistent clinical arthritis, the overall results did not demonstrate a difference between the groups. The results were also stratified according to high/low risk and ACPA positivity. Dr Krijbolder highlighted that indeed among the high-risk patients, 70% of those on placebo advanced to clinical arthritis. "In the treatment group, this is clearly less at first, with a statistically significant difference at 6 and 12 months, but during the second year this disappeared, so this implicates a delay in arthritis development but no prevention," she declared. This was similar for the ACPA-positive subgroup. However, the picture was different when the focus was on pain: the reduction in pain was more pronounced in those on methotrexate (P<0.05) and it not only lasted for the time of therapy but also during the subsequent year of follow-up without medication. Furthermore, a significant and equally persistent decrease in disease burden was observed in measures like morning stiffness, functional impairment, and presenteeism at work, in addition to MRI-detected joint inflammation.

Dr Krijbolder described the results as somewhat counter-intuitive since there was a delay in the development of arthritis but no definite prevention. Thus, to further elucidate these results, a post-hoc analysis of the high-risk partakers was executed. "Participants who did not progress to arthritis had an almost complete relief of pain and nearly returned to the normal range of MRI-detected inflammation that can be found in symptom-free controls," Dr Krijbolder revealed. "Participants who did progress, whether it was early or late during follow-up, clearly had less pain and less MRI-detected inflammation if they were in the treatment group." Therefore, her take-away was that both non-progressors and progressors were benefiting from this treatment.

"For the first time, we found proof for the concept of disease modification when intervening in pre-RA," she concluded.


Risk factors for dementia in RA patients discovered

For patients with rheumatoid arthritis (RA), swelling of large joints, rheumatoid nodules, hypertension, cardiovascular (CV) disease, and depression were recognised risk factors for dementia. The analysis of a Minnesotan cohort found an about 2-fold elevated risk of dementia in case those factors were present.

What are the risk factors for developing dementia in patients with RA? The goal of a population-based inception cohort study conducted by a group of Mayo Clinic investigators was to elucidate this question [1]. "Our recent studies from population-based cohorts in Olmsted County have shown that even though the overall risk of dementia is increased in patients with RA as compared with the non-RA population, there has been a decline in its incidence in recent decades coinciding with improved control of RA," Prof. Elena Myasoedova (Mayo Clinic, MN, USA) reported in her presentation. The study included 886 patients ≥50 years who resided in Minnesota and were diagnosed with RA between 1980 and 2014. Follow-up was performed until the end of 2019. For the attribution of incident dementia, at least 2 ICD codes for dementia had to be present ≥30 days apart. Two different Cox proportional hazard models were fitted with model 1 adjusting for age, sex, and year of RA incidence. The other model also included CV risk factors as well as any CV disease.

The mean age of the cohort was 65 years, nearly two thirds were women, and the median follow-up was 8.5 years. During this time, 103 cases of incident dementia occurred. After RA was diagnosed, the risk for dementia rose gradually (2–3% over 5 years). "Similar to the general population, age was one of the risk factors that has been noticed, and older age of RA incidence was associated with a higher incidence...
of dementia," Prof. Myasoedova reported. Furthermore, the presence of rheumatoid nodules at baseline and swelling of large joints or anxiety at any time carried an around 2-fold risk-augmentation for dementia. Depression at baseline or ever was an even stronger risk factor with a hazard ratio (HR) between 2.23 and 2.76 depending on timing and model. "Out of the CV risk factors, hypertension stood out for association with dementia," Prof. Myasoedova remarked. The HRs for baseline hypertension were 1.84 (model 1) and 2.79 (model 2). Among the CV events, baseline heart failure (HR 2.72 and 2.89) and ever ischaemic stroke (HR 3.16 and 3.28) were especially linked to dementia in RA patients in both models. Among the factors that were not associated with dementia were sex, race, education, and RA disease characteristics.

"In summary, clinically active disease as well as hypertension, CV events, depression, and anxiety increased the risk of dementia among patients with RA. Among CV events, ischaemic stroke and heart failure were particularly associated with the risk of dementia," Prof. Myasoedova concluded. Further studies in this space including the impact of non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic, biologic, and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) will add to this emerging story.


VTE in global registry data more common in JAK inhibitor-treated RA patients

The occurrence of major cardiovascular events (MACEs) and venous thromboembolism (VTE) in JAK inhibitor-treated patients with rheumatoid arthritis (RA) was the focus of a large register-based study. It found an increase of VTE with JAK inhibition, as well as MACEs, the latter only in cases reported by physicians.

"With the recently published ORAL Surveillance study, some concerns have been raised about cardiovascular and thromboembolic risks associated with tofacitinib in comparison to anti-TNF," Prof. Adeline Ruyssen-Witrand (Toulouse University Hospital, France) said, referring to a post-authorisation trial in older patients with RA (NCT02092467) [1,2]. Due to these safety warnings, the French study analysed data from The World Health Organization Global Individual Case Safety Report (VigiBase®), which encompasses worldwide data on side effects [1]. In VigiBase®, physicians and non-physicians can submit cases. Prerequisites for case selection were patients with RA aged 18–75 years, who had adverse events related to JAK inhibitors or anti-TNF medication. MACEs, i.e. myocardial infarction, stroke, and cardiovascular death, as well as VTE in terms of pulmonary embolism and deep vein thrombosis, were classified as events of interest. Out of 16 million declared cases between 2011 and 2022, 50,694 were RA patients on JAK inhibitors, and 239,914 received anti-TNFs.

The analysis revealed MACEs in 817 JAK inhibitor-treated patients and 3,379 patients treated with anti-TNF, with 23% and 33% registered by physicians, respectively. As for VTE, reports were found in 596 and 818 cases in patients treated with JAK inhibitors and anti-TNFs, respectively, with 46% and 38% entering the database upon physician notification. Overall, most patients were 60 years of age or older.

The study found no increase in MACEs with JAK inhibition in the disproportionality analysis in the entire population. "However, after stratification on the source of reporting, meaning physician versus non-physician, we could observe a slight increase of reported MACEs with JAK inhibitors in comparison with anti-TNF, as well as an increase of myocardial infarction, in the physician reports," Prof. Ruyssen-Witrand said. This was significantly indicated by adjusted reporting odds ratios (ROR) of 1.45 (MACEs) and 1.70 (myocardial infarction) in the physician-reported subgroups.

Regarding VTE, an increased risk associated with JAK inhibitors was found in the main analysis (ROR 3.48) and also after stratification according to physician (ROR 8.51) and non-physician reports (ROR 1.96). At further stratification according to the date of declaration in VigiBase®, there was an increase after the authority alerts. However, Prof. Ruyssen-Witrand underlined that in the year prior to these alerts, the study results already revealed an increase in risk for the 2 events with JAK inhibitors compared with anti-TNFs, with an odds ratio of 1.24 for MACEs and 1.84 for VTE.

Nonetheless, the selective outcome reporting might be a study limitation, giving a negative bias against JAK inhibitors. Prof. Ruyssen-Witrand concluded that this kind of analysis can be very useful for clinicians to detect early safety signals after a new drug marketing use, especially when focusing on physician-declared cases.

How to treat enthesitis in 2022

Therapy of enthesitis has clearly advanced over the previous decades. Many biologics have shown to be effective in the resolution of enthesitis, without clear evidence that one class of drug is superior to the other, which was discussed at a EULAR How to Treat session.

Enthesitis is defined as inflammation at the site of insertion of muscle or tendon in the bone. It is often located at the Achilles tendon, plantar fascia, elbows, and costochondral joints. However, it may be ubiquitous, which might be challenging to recognise. As Prof. Dennis McGonagle (University of Leeds, United Kingdom) emphasised, enthesitis has a major impact on activities of daily living in patients with psoriatic arthritis (PsA) [1]. This has been shown in the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey that examined the influence of PsA on patients’ activities of daily living and unmet treatment needs [2]. It showed that enthesitis can impede walking outdoors on flat ground or bending down to pick up clothing from the floor.

In spondyloarthritis (SpA), chronic synovitis potentially results in bone and cartilage erosion analogous to rheumatoid arthritis [3]. However, enthesitis may be the first abnormality to trigger an inflammatory response in the synovium of SpA patients. Therefore, synovitis in SpA is secondary to the liberation of proinflammatory mediators from the enthesis, resulting in enthesal erosions and periarticular abnormalities, whereas the synovitis of rheumatoid arthritis is primary [3]. Mechanical stress plays an important role in the enthesitis pathogenesis, with the disease subsequently spreading to adjacent joint structures, including the synovium and bone. Common enthesitis features also target organs of SpA beyond the joint and explain comorbid conditions like nail and skin psoriasis, inflammatory bowel disease, and uveitis. Sites of repetitive stress are, for example, nail attachments, psoriatic skin lesions over knees and elbows, lesions in the ileocecal junction, or the ciliary body. Not only are there anatomical and biomechanical similarities between the enthesis and these other structures but there is emerging evidence for similar resident immune cell populations, including IL-23R positive cells at all of these sites [4].

As Prof. McGonagle pointed out, in clinical trials, enthesitis is assessed with the Maastricht AS Enthesitis Score (MASES) including 13 sites or the Spondyloarthritis Research Consortium of Canada (SPARCC) assessing 16 sites [5]. However, in clinical trials, the Leeds Enthesitis Index (LEI), designed for use in PsA, evaluates tenderness at 6 sites: lateral epicondyles of the humerus, medial condyles of the femur, and the insertion of the Achilles tendon. “As there are only 6 sites, this is really fast to do,” Prof. McGonagle said [1].

Therapy of enthesitis: much to consider

A couple of general considerations should precede the choice of therapy. In inflammatory enthesitis, mechanical components must be identified and treated, just as inflammatory components should not be overlooked in mechanical disease. Different sites of isolated enthesitis may require different physical therapy and medication strategies, such as the use of intra-enthesis corticosteroids, or not. The location of enthesitis plays a major role in “site-specific” physical therapy strategies. Finally, patients should be informed that enthesitis is often linked to good tissue or excessive tissue repair rather than progressive joint destruction that is evident with synovitis.

Until recently, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) were not recommended by EULAR to treat enthesitis [6]. However, the SEAM-PsA trial (NCT02376790) changed this view. This phase 3, randomised, double-blind study included 851 participants with PsA and aimed to examine the efficacy of methotrexate monotherapy compared with etanercept monotherapy and the value of combining methotrexate and etanercept [7]. In this trial, etanercept monotherapy and combination therapy showed greater efficacy than methotrexate monotherapy. However, even with methotrexate monotherapy, 50.7% of participants achieved an ACR20 response with an enthesitis resolution in 43.5% of cases [7]. Furthermore, “Methotrexate is actually linked to non-evolution to PsA when used in subjects with psoriasis,” added Prof. McGonagle. This was recently shown in a retrospective study, where the incidence of PsA in patients with psoriasis was assessed according to different treatments for their skin: topics/no treatment, csDMARDs, and biological DMARDs (bDMARDs). During follow-up, the incidence of PsA was lowest in patients treated with biological agents (1.9%),

Enthesitis is defined as inflammation at the site of insertion of muscle or tendon in the bone. It is often located at the Achilles tendon, plantar fascia, elbows, and costochondral joints. However, it may be ubiquitous, which might be challenging to recognise. As Prof. Dennis McGonagle (University of Leeds, United Kingdom) emphasised, enthesitis has a major impact on activities of daily living in patients with psoriatic arthritis (PsA) [1]. This has been shown in the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey that examined the influence of PsA on patients’ activities of daily living and unmet treatment needs [2]. It showed that enthesitis can impede walking outdoors on flat ground or bending down to pick up clothing from the floor.

In spondyloarthritis (SpA), chronic synovitis potentially results in bone and cartilage erosion analogous to rheumatoid arthritis [3]. However, enthesitis may be the first abnormality to trigger an inflammatory response in the synovium of SpA patients. Therefore, synovitis in SpA is secondary to the liberation of proinflammatory mediators from the enthesis, resulting in enthesal erosions and periarticular abnormalities, whereas the synovitis of rheumatoid arthritis is primary [3]. Mechanical stress plays an important role in the enthesitis pathogenesis, with the disease subsequently spreading to adjacent joint structures, including the synovium and bone. Common enthesitis features also target organs of SpA beyond the joint and explain comorbid conditions like nail and skin psoriasis, inflammatory bowel disease, and uveitis. Sites of repetitive stress are, for example, nail attachments, psoriatic skin lesions over knees and elbows, lesions in the ileocecal junction, or the ciliary body. Not only are there anatomical and biomechanical similarities between the enthesis and these other structures but there is emerging evidence for similar resident immune cell populations, including IL-23R positive cells at all of these sites [4].

As Prof. McGonagle pointed out, in clinical trials, enthesitis is assessed with the Maastricht AS Enthesitis Score (MASES) including 13 sites or the Spondyloarthritis Research Consortium of Canada (SPARCC) assessing 16 sites [5]. However, in clinical trials, the Leeds Enthesitis Index (LEI), designed for use in PsA, evaluates tenderness at 6 sites: lateral epicondyles of the humerus, medial condyles of the femur, and the insertion of the Achilles tendon. “As there are only 6 sites, this is really fast to do,” Prof. McGonagle said [1].

Therapy of enthesitis: much to consider

A couple of general considerations should precede the choice of therapy. In inflammatory enthesitis, mechanical components must be identified and treated, just as inflammatory components should not be overlooked in mechanical disease. Different sites of isolated enthesitis may require different physical therapy and medication strategies, such as the use of intra-enthesis corticosteroids, or not. The location of enthesitis plays a major role in “site-specific” physical therapy strategies. Finally, patients should be informed that enthesitis is often linked to good tissue or excessive tissue repair rather than progressive joint destruction that is evident with synovitis.

Until recently, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) were not recommended by EULAR to treat enthesitis [6]. However, the SEAM-PsA trial (NCT02376790) changed this view. This phase 3, randomised, double-blind study included 851 participants with PsA and aimed to examine the efficacy of methotrexate monotherapy compared with etanercept monotherapy and the value of combining methotrexate and etanercept [7]. In this trial, etanercept monotherapy and combination therapy showed greater efficacy than methotrexate monotherapy. However, even with methotrexate monotherapy, 50.7% of participants achieved an ACR20 response with an enthesitis resolution in 43.5% of cases [7]. Furthermore, “Methotrexate is actually linked to non-evolution to PsA when used in subjects with psoriasis,” added Prof. McGonagle. This was recently shown in a retrospective study, where the incidence of PsA in patients with psoriasis was assessed according to different treatments for their skin: topics/no treatment, csDMARDs, and biological DMARDs (bDMARDs). During follow-up, the incidence of PsA was lowest in patients treated with biological agents (1.9%),
followed by those treated with csDMARDs (6%), and as high as 16.6% in patients treated with topical therapy only [8]. Therefore, in the updated GRAPPA 2021 recommendations on PsA, methotrexate can be used to treat enthesitis [9]. Other csDMARDs including sulphasalazine need revisiting and overall more work is needed in this space to determine its role in a predominant enthesitis pattern of PsA or SpA.

Efficacy of IL-17 and IL-23 blockers

The anti-TNF agents have been used for over a decade to treat enthesitis and the question that has recently been addressed is whether the IL-23/17 axis cytokine blockade might be better for enthesitis. IL-17 inhibitors can be used to treat enthesitis. In the open-label, head-to-head trial SPIRIT-H2H (NCT03151551), ixekizumab was superior to adalimumab regarding the resolution of enthesitis at week 24, and numerically superior at week 52, even though this was not the primary outcome [10,11]. Moreover, IL-23 blockers have shown to be efficacious in treating enthesitis [12]. However, in the double-blind, phase 3, EXCEED trial (NCT02745080), resolution rates of enthesitis were similar when secukinumab was compared with adalimumab [13]. In a network meta-analysis of phase 3 studies on the PsA treatment, the efficacy and safety of different DMARDs were compared, with a special focus on bDMARDs [14]. According to this analysis, guselkumab, IL-17 inhibitors (secukinumab, ixekizumab, brodalumab), and adalimumab were similarly efficacious in the resolution of enthesitis (see Figure). “Although this is not clear yet, IL-17 and IL-23 blockers might be more efficacious than TNF-blockers,” Prof. McGonagle said. Head-to-head studies comparing different mechanisms of action with enthesitis resolution as the primary outcome will be needed to evaluate this.

Microinflammation and healing are common in enthesitis. “That is why alternative medicine and placebo do so well,” Prof. McGonagle said. This reflects the normal cycle of microdamage and subsequent tissue repair responses. For the physician asking the question of what is the best agent to treat a predominant enthesitis pathology, Prof. McGonagle concluded: “There is no clear evidence that one class of drug is superior to another in the therapy of enthesitis, but further research is needed.”

Baseline cardiovascular risk linked to higher rates of MACE in PsA and PsO patients receiving tofacitinib

Post-hoc trial data revealed that rates of major adverse cardiovascular events (MACE) and malignancies in patients with psoriatic arthritis (PsA) and psoriasis (PsO) receiving tofacitinib vary according to their baseline cardiovascular events (MACE) and malignancies in PsA and PsO patients receiving tofacitinib vary according to their baseline atherosclerotic cardiovascular (CV) risk. Patients with intermediate and high baseline risk were predisposed to a higher incidence of events.

PsA and PsO are linked to an increased burden of CV and metabolic comorbidities, and an association between CV disease and future development of malignant tumours has been described [1-4]. Recent concerns about the cardiovascular safety associated with JAK inhibitors in patients with rheumatoid arthritis have arisen. To explore this issue further, Prof. Lars Erik Kristensen (Copenhagen University Hospital, Denmark) and his fellow researchers performed a post-hoc analysis regarding patients with PsA and PsO treated with tofacitinib [1]. The analysed data comprised 3 PsA and 7 PsO trials of phase 2 and 3, as well as open-label extensions. Outcomes were defined as incidence rates for MACE and malignancies, the latter excluding non-melanoma skin cancer. Risk stratifications were performed according to the history of coronary artery disease, the baseline 10-year risk of atherosclerotic CV disease, and baseline metabolic syndrome. The follow-up lasted until
the occurrence of the first event or 28 days after the last administration of tofacitinib.

Overall, 783 PsA patients with 2,038 patient-years of tofacitinib exposure and 3,663 PsO patients with a total exposure of 8,950 patient-years were included. Median exposure time was 3.0 and 2.4 years in patients with PsA and PsO, respectively. History of coronary artery disease was present in 5% and 2.5%, as well as baseline metabolic syndrome in 40.9% and 32.7%, respectively. The patients without coronary artery disease were stratified in correspondence to their baseline atherosclerotic CV disease risk, according to the Pooled Cohort Equations calculator, and more than 20% turned out to be in the intermediate or high-risk category.

The incidence rates for MACE in PsA patients ranged from 0.1 (95% CI 0.0–0.4) to 1.3 (95% CI 0.0–7.0), with increasing values associated with increasing baseline atherosclerotic CV risk. The presence of baseline metabolic syndrome was linked to an incidence rate of 0.6 (95% CI 0.2–1.4). “For PsO patients, we saw the same pattern, also an increasing incident rate with increasing background risk,” Prof. Kristensen explained. He put these results into perspective by pointing out some imprecision due to rather low amounts of events leading to wide confidence intervals of the incidence rates, both for MACE and malignancies. Indeed, in terms of malignancies, the highest incidence rates were observed in patients with intermediate (PsA: 2.5 [95% CI 1.1–4.9] and PsO: 1.3 [95% CI 0.8–1.9]) and high (PsA: 1.3 [95% CI 0.0–7.0] and PsO: 3.6 [95% CI 2.0–5.9]) atherosclerotic CV risk (see Figure). The numerically higher rates for PsO related to greater drug exposure in terms of patient-years.

“This further stresses that we should look beyond the disease targets, the skin and the joints. We should also care about comorbidities, especially cardiovascular ones, and treat those. I think we, as rheumatologists should be in the centre and be responsible, we might delegate to primary care and so on, but it is an important outcome,” Prof. Kristensen stressed in his conclusion.


**Treat-to-target dose reduction effective in spondyloarthritis**

Many patients with psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) need long-term treatment with biologics, which causes considerable costs and might be responsible for an elevated risk of infection. In an open-label, randomised, non-inferiority trial, tapering TNF blockers in patients that achieved remission or at least low disease activity led to a similar proportion of patients still in low disease activity after a year and a 46% lower risk of grade 3 and 4 infections.

“What makes our trial relevant? First, we focused on stepwise tapering instead of fixed-dose tapering. Secondly, we used disease-specific targets,” explained Dr Celia Michielsens (Sint Maartenskliniek, the Netherlands). Together with her team, she investigated whether a treat-to-target (T2T) strategy with tapering is non-inferior (with a pre-specified
non-inferiority margin of 20%) compared with a T2T strategy without tapering in a randomised, controlled, open-label, non-inferiority trial [1]. All participants used TNF inhibitors and had stable low disease activity for ≥6 months. They were randomised (2:1) to a T2T tapering or no-tapering strategy and were followed for 12 months. Low disease activity was defined as a Psoriatic Arthritis Disease Activity Score (PASDAS) ≤3.2 for PsA, and/or Ankylosing Spondylitis Disease Activity Score (ASDAS) <2.1, and/or judgement of physician and patient.

Of the 81 participants in the tapering group, 52% had PsA and the rest had axSpA. Of the 41 participants in the non-tapering group, 54% had PsA and the rest axSpA. At 12 months, 73% in the non-tapering group and 69% in the tapering group achieved low disease activity. This difference was well below the inferiority margin, thus confirming non-inferiority. At 12 months, 58 (72%) participants of the tapering group were successfully tapered. The only disadvantage of this approach was an increase in the use of other medications in the tapering group, a difference that was statistically significant regarding non-steroidal anti-inflammatory drug use (54% vs 24%; P=0.002). However, the risk of grade 3/4 infections was 46% lower, and the risk of injection site reactions was 23% lower in the tapering compared with the non-tapering group.

Taken together, there was no significant difference between a tapering and a non-tapering approach regarding disease activity. "This might have been because we used not a fixed but an individualised tapering approach," Dr Michielsen said. Moreover, tapering led to a substantial reduction in TNF inhibitor use.


A novel oral treatment possibility for non-radiographic axSpA on the horizon

Although both TNF blockers and cytokine blockers have shown to be effective in spondyloarthritis, there is an ongoing demand for other treatment modalities. In the SELECT-AXIS 2 trial, once-daily oral therapy with upadacitinib showed to be markedly effective and well-tolerated in patients with active, non-radiographic axial spondyloarthritis (nr-axSpA) at week 14.

The JAK pathway is a potential therapeutic target in spondyloarthritis and could become an effective new oral treatment. Previously, upadacitinib has shown its efficacy and safety in the phase 2/3 SELECT-AXIS 1 trial (NCT03178489), which evaluated the JAK inhibitor in biologic-naive participants with active ankylosing spondylitis [1]. Both TNF blockers and IL-17 blockers have shown to be effective in nr-axSpA. "Having another mode of action, and not directly against a single cytokine but an inflammatory pathway, might be useful," said Prof. Filip van den Bosch (Ghent University, Belgium) [2].

The SELECT-AXIS 2 trial (NCT04169373) was separated into 2 studies according to whether participants had ankylosing spondylitis with an inadequate response to biologic disease-modifying antirheumatic drugs (bDMARDs) or nr-axSpA with objective signs of inflammation. Prof. van den Bosch presented the study part including participants with nr-axSpA: adults with a clinical diagnosis of nr-axSpA who also fulfilled the 2009 Assessment of SpondyloArthritis International Society (ASAS) classification criteria were treated with upadacitinib 15 mg once daily (n=157) or placebo (n=157). "According to a central reading, participants did not meet the radiologic criterion of modified New York criteria but had signs of active disease, namely elevated C-reactive protein concentrations or sacroiliitis in MRI," Prof. van den Bosch explained. About a third of participants were previously treated with bDMARDs (i.e. TNF blockers or IL-17 inhibitors), and all had shown an inadequate response to ≥2 non-steroidal anti-inflammatory drugs (NSAIDs).

After 14 weeks, 45% of participants randomised to receive upadacitinib achieved the primary endpoint (i.e. ASAS40 response) compared with 23% of those assigned to placebo (P<0.0001). "I have 3 take-home messages here: there was a clear difference between upadacitinib and placebo, the absolute difference is in the ballpark of other biologics (around 40% and 50%), and, lastly, we saw a fast response with a separation of curves already at week 2," Prof. van den Bosch commented.

Upadacitinib was also superior in many other multiplicity-controlled secondary endpoints, including change from baseline in patient’s assessment of total back pain, Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Quality of Life (ASQoL), and MRI Spondyloarthritis Research Consortium of Canada (SPARCC) score for sacroiliac joint inflammation.

Overall, the safety profile of upadacitinib was consistent with what has been observed with other inflammatory
musculoskeletal diseases, and no new risks were identified. Adverse events were reported in 48% and 46% of participants in the upadacitinib and placebo arms, respectively. No deaths or major adverse cardiovascular events were observed during 14 weeks of treatment with the JAK inhibitor.

**Similar efficacy in ankylosing spondilitis patients**

The results of the second part of the SELECT AXIS 2 study, including 420 participants with ankylosing spondylitis, were revealed in a poster tour presentation by Prof. Désirée van der Heijde (Leiden University Medical Center, the Netherlands) [3]. “This is the first clinical trial to assess the efficacy and safety of a JAK inhibitor in an active ankylosing spondylitis population with an inadequate response to bDMARDs,” Prof. van der Heijde emphasised.

Significantly more participants achieved the primary endpoint of ASAS40 response at week 14 with upadacitinib versus placebo (45% vs 18%; P<0.0001). The onset of effect was already noted at week 4. Moreover, all secondary endpoints met statistical significance in favour of upadacitinib across multiple clinical domains of ankylosing spondylitis, e.g. ASDAS, BASFI, and sacroiliac joint inflammation on MRI [3].

Treatment-emergent adverse events from baseline to week 14 were similar in the upadacitinib and placebo arms (41% compared with 37% in the placebo group), and there were no new safety signals.


Many RA and PsA patients have problems with their sex life

A Spanish study revealed that patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) suffer more often from sexual dysfunction compared with a healthy population. Older age, unemployment, and lower income are all risk factors.

Data from a cross-sectional, observational study suggests patients with PsA were at 8 times greater risk of sexual dysfunction, and patients with RA were at 10 times greater risk when compared with their healthy counterparts [1].

Although previous studies hinted at a higher frequency of sexual dysfunction in RA and PsA, most were of low quality regarding the study design. “Most studies lack a control group,” said Dr Carlos Valera-Ribera (Doctor Peset University Hospital, Spain). Therefore, he and his team performed a study in which patients diagnosed with PsA and RA were compared with a control group of healthy individuals. Included were 188 adult patients of any sexual orientation in 2 different university hospitals. The researchers collected different variables, including age, sex, year of diagnosis, perceived health, marital status, level of education, income, history of depression, and treatment for mental health disease. All participants completed the 14-item Changes in Sexual Functioning Questionnaire (CSFQ-14), a standardised questionnaire used to evaluate changes in sexual function due to disease or medication in 4 different domains: pleasure, desire, arousal, and orgasm. A regression model was created to estimate the influence of the collected variables on the obtained results.

Of the 188 participants (52.7% women), 72 had a diagnosis of PsA and 27 of RA. They were compared with 89 healthy individuals matched by age (mean 48 ± 12.5 years). More than half of the participants assessed their own health as “good” or “very good”. Interestingly, 77.7% had a personal history of depression, which did not correlate significantly with sexual dysfunction. In contrast, older age, unemployment, and low income were factors associated with the risk of sexual dysfunction, consistent with earlier findings from studies including patients with rheumatic diseases. “All the domains of the sexual sphere were functionally deteriorated,” Dr Valera-Ribera said.

Around 80% of the participants were in a relationship. Nearly half of patients with RA (48.2%) experienced sexual dysfunction compared with 30.4% in the PsA group and only 5.9% in the control group. All the domains of the CSFQ-14 questionnaire were negatively affected by being diagnosed with PsA or RA (P<0.001). In general, men were more severely affected. The odds ratio of sexual dysfunction was 8.7 times higher in PsA patients and 10 times higher in RA patients.

Dr Valera-Ribera concluded that sexual health must be considered a holistic part of care. The CSFQ-14 is a valuable tool for the management of sexual health in people with inflammatory rheumatic diseases.

New treatments in osteoarthritis

Osteoarthritis (OA) pathogenesis is complex. According to novel data, the compressive load repair pathway is beneficial for the cartilage. Therefore, future research should rather focus on cartilage regeneration instead of fighting inflammation.

As Prof. Tonia Vincent (University of Oxford, United Kingdom) pointed out in her talk, “Stop taking painkillers for arthritis” was a depressing headline published a month ago in The Times. It was based on the draft NICE guidelines released in April 2022 [1]. In the guidelines, exercise for OA patients is recommended instead of pain medication, as several control trials stated that any exercise was beneficial compared with no exercise. There is less established data on a dose-dependent relationship between OA and weight loss. The 2 large existing cohort studies are of low to very low quality. In the United Kingdom, it is recommended to commence topical NSAIDs and intra-articular injections but not to offer other pain medications as these are not deemed to be cost-effective.

Drugs used in inflammatory arthritis failed in OA

OA occurs due to both anabolic and catabolic processes. Previously, research targeted the catabolic process, aiming at dampening immune responses or attacking specific proteases in this pathway. Therefore, some drugs used in inflammatory arthritis (i.e., DMARDs, anti-IL1, anti-IL6, anti-TNF, hydroxychloroquine) were repurposed for OA, but unfortunately, all studies in this regard have failed. However, as Prof. Vincent said: “There is still hope for OA patients in the future!”

Over the past 20 years, revolutionary progress has been made in the OA field, particularly in epidemiology and molecular analysis of articular cartilage, as well as tremendous improvements in Omics studies. However, the way forward is hindered by the high costs of setting up a clinical trial, so more attention is now given to experimental outcomes rather than clinical outcomes, where smaller numbers of patients are necessary.

OA: driven by mechanical injury

OA is a disease driven by abnormal mechanical load going through both large and small joints. This is due to 2 mechanisms: increased load on a normal joint, by obesity or malignment, or, alternatively, normal load on a joint that has lost its mechano-protection due to ageing or an acute joint injury.

The articular cartilage consists of 5–10% of the total tissue volume of the joint and is one of the most quiescent tissues of the human body. Cartilage is exquisitely sensitive to injury. When an injury occurs, almost every signalling pathway in the cartilage is rapidly activated within 30 seconds. Injury response genes, including inflammatory and anti-inflammatory repair genes, are turned on, producing various proteins. “We think this injury response is really important to what happens in OA,” Prof. Vincent said.

Pathogenesis is a balance of 2 counteracting pathways

Further research has shown the existence of 2 principal pathways that drive different responses in the joint (see Figure):

- The sheer stress pathway, resulting in mechano-inflammation leading finally to matrix degradation and pain;
- The repair pathway, releasing a whole host of growth factors that collectively drive the repair and regeneration of the cartilage. Therefore, the compressive load might be beneficial for the cartilage.

Research shows that all 70–80 genes directly associated with OA biology activate the repair pathways. “Maybe we have been barking up the wrong tree. Maybe we should be focusing our attempts at repairing cartilage rather than suppressing inflammation in OA,” Prof. Vincent said.
The compelling evidence to support the hypothesis that articular cartilage can undergo spontaneous repair and regeneration is 2-fold:

• In a knee joint distraction procedure, joints were pulled apart using an external fixator kept in situ for 6 weeks, and patients were allowed to walk, meaning there would be modest compressive load on joints but no shear stress, as the joints were not hinged. After 2 years of follow-up, cartilage-like tissue was seen in all 20 patients in T2-weighted MRI, as well as a significant reduction in the eroded joint surface [2].

• Intraarticular injections of sprifermin, a recombinant human fibroblast growth factor, resulted in a dose-dependent increase in cartilage thickness [3,4]. Although a post-hoc analysis found no improvement in pain in patients who had already progressed in OA, there was a dose-dependent pain suppression in patients at high risk of progression [5].

Some future pro-regenerative therapies are on the horizon. An interesting candidate is LNA043, an angiopoietin-like 3 agonist. After robust preclinical data, this agent is currently being assessed in 2 clinical trials. The jury is still out regarding GLPG1972, a highly selective aggrecanase inhibitor, and the senolytic UBX0101, but neither agent met the primary endpoint of their respective trials. Phase 3 results on lorecivivint will be presented later this year.

Choose studies wisely in OA
To enhance future success, it is imperative to optimise clinical outcomes. “It is really important not to throw the baby out with the bathwater, because we are choosing the wrong primary and secondary endpoint in these studies,” Prof. Vincent said. Maintaining momentum in OA research is also essential, as many new avenues are opening. Finally, patient stratification in clinical trials is necessary, as more evidence has uncovered that different OA patients respond differently to treatment.

In an exploratory analysis of the CANTOS trial (NCT01327846), a surprisingly significant 50% reduction in joint replacements in patients treated with any dose of the IL-1 inhibitor canakinumab was observed [6]. Although this requires much deeper investigation, hope can be placed for the future. Another study showed that patients with low levels of collagen type II show a significant reduction in the eroded joint surface [2].

**OA associated with alcohol and drug abuse**
Obesity and back pain are well-known comorbidities of osteoarthritis (OA). A study revealed that comorbidities of OA are much more diverse and include conditions such as anaemia, cataract, and hearing loss, but also a higher risk for addiction.

Although previous studies have already shown that patients with OA have a higher risk of developing comorbidities, many focused on only 1 or a few conditions. As Dr Anne Kamps (Erasmus University Medical Center, the Netherlands) pointed out, 1 in 4 adults with OA has ≥2 chronic conditions, which is a considerable burden on the healthcare system and the quality-of-life [1]. “We wanted to determine the risk of comorbidity after incident diagnosis of hip or knee OA compared with individuals with no prior diagnosis of OA,” said Dr Kamps. Together with her team, she used an integrated primary care information database from general practices with >2.5 million patients from the Dutch population.

The study population consisted of over 1.8 million patients and examined 58 comorbidities. Overall, patients previously diagnosed with OA had an increased risk of a subsequent diagnosis in about 50% of comorbidities studied. Moreover, the wide variety of comorbidities included not only known cardiovascular factors, such as obesity or other musculoskeletal diseases such as gout, back and neck pain, but also anaemia, cataracts, chronic kidney disease, coronary heart disease, hearing loss, sleep disorders, and thromboembolic disease. In OA patients, the largest associations were found for obesity (HR 2.55), fibromyalgia (HR 2.06), polymyalgia (HR 1.72), drug abuse (HR 1.40), and rheumatoid arthritis (HR 1.52). Particularly in patients with hip OA, the largest positive associations were noticed with polymyalgia rheumatica (HR 1.81), fibromyalgia (HR 1.70), spinal disc herniation (HR 1.64), thromboembolic disease (HR 1.47), and alcohol abuse (HR 1.44).

“Whereas associations with obesity and other musculoskeletal conditions were known previously, we found remarkable and less known associations that should be starting points for...
future research,” Dr Kamp said. Further studies should evaluate whether these comorbidities are prevalent due to shared risk factors or a result of the OA.


**Body mass index increase associated with structural changes in knee OA**

Both the incidence and structural defects of knee osteoarthritis (OA) can be slowed down by a reduction of the body mass index (BMI). Even a moderate weight loss is beneficial in this respect.

Obesity is a known risk factor for OA and is associated with progression of knee OA. “But what we don’t know is whether weight loss is associated with a decreased incidence of knee OA in men and decreased progression of knee OA in men and women,” Dr Zubeyir Salis explained (University of New South Wales, Australia). Therefore, his study aimed to define the association between change in weight and the incidence and progression of radiographic knee OA [1].

Scores from knee radiographs at baseline and at 4 to 5 years of follow-up were obtained from 3 independent data sets (2 from the USA and 1 from the Netherlands). The exposure of interest was the change in BMI from baseline to 4 to 5 years of follow-up. To investigate the incidence of structural defects of knee OA, the researchers selected a total of 9,732 knees with a Kellgren-Lawrence (KL) grade of 0 (none) or 1 (doubtful) at baseline, named the incidence cohort, and determined the odds of having a KL grade at follow-up of 2 (minimal), 3 (moderate), or 4 (severe). To investigate progression, 6,084 knees were assessed with a KL grade at baseline of 2, 3, or 4 (the progression cohort), and the odds of increasing by 1 or more KL grades at follow-up were determined. “We also looked at the degeneration of individual radiographic features (i.e. joint space narrowing and osteophytes on the femoral and tibial surface) on the medial and lateral sides of the knees in both cohorts,” Dr Salis said. Here, degeneration was defined as an increase by 1 or more Osteoarthritis Research Society International (OARSI) grades.

Included were 4,842 participants in the incidence cohort and 3,216 participants in the progression cohort. Change in BMI was positively associated with both the incidence and progression of knee OA. “The change in BMI was also positively associated with narrowing of joint space on the medial but not the lateral compartment of the knee. However, there was no association between the change in BMI and osteophytes in both compartments,” Dr Salis commented.

These results could have an important public health impact. “We estimated that those who lost 1 BMI unit could reduce the incidence of knee radiographic OA by 13% and the progression of knee OA by 10%,” Dr Salis concluded.


What Is New in Lupus and Scleroderma?

**Inhibition of Bruton’s tyrosine kinase: a new way of approaching SLE?**

In a dose-finding study, orelabrutinib demonstrated promising results as a future treatment option in systemic lupus erythematosus (SLE). Good overall tolerability and greater response rates were observed compared with placebo.

Orelabrutinib is an oral drug that selectively inhibits Bruton’s tyrosine kinase (BTK). It already has approval for the treatment of B-cell cancer in China and is currently under investigation for several other indications [1,2]. Prof. Zangou Li (Peking University People’s Hospital, China) presented data of a phase 1b/2a, randomised, double-blind, placebo-controlled, dose-finding study (NCT04305197) on orelabrutinib in adult patients with an SLE Disease Activity Index 2000 (SLEDAI-2K) ≥5 and positive testing for autoantibodies [1]. Besides safety and tolerability results that were the trial’s primary objectives, the researchers were also interested in the pharmacokinetics, pharmacodynamics, and preliminary efficacy.
All 60 randomised participants had been on a stable standard-of-care therapy at least 3 months before the trial started. Within 4 study groups, the participants were assigned to either placebo or 1 of 3 different dosages of the study drug: daily orelabrutinib 50 mg, 80 mg, and 100 mg over 12 weeks. Due to the study phase and design, there was no possibility of formal hypothesis testing.

"Based on the clinical features and the laboratory parameters, there was not much difference between the groups," Prof. Li pointed out regarding the baseline characteristics. The mean age at baseline was 33.7 years, and 96.7% were women. In the different study arms, between 85.7% and 93.3% had a background treatment of corticosteroids, 80% to 86.7% took hydroxychloroquine, and 57.1% to 80% immunosuppressive agents. All doses of orelabrutinib induced a BTK occupancy that was nearly 100% over 24 hours. The drug demonstrated a half-life of 4 hours and an increasing plasma exposure according to dosage.

Prof. Li stated that the safety data was mostly similar between the groups. Overall, adverse events were mainly mild to moderate. Serious treatment-emergent adverse events only happened in the 80 mg and 100 mg study drug arms in 26.7% and 12.5% of participants, respectively. Furthermore, a decrease in lymphocytes was also more frequent in these arms: 40.0% and 31.3% versus 7.1% (placebo) and 13.3% (50 mg dosage), respectively.

As for clinical results, orelabrutinib led to numerical higher response rates in the SLE Responder Index (SRI) 4, compared with placebo: 35.7% (placebo), 46.7% (50 mg), 53.3% (80 mg) and 56.3% (100 mg). In participants with severe disease (SLEDai-2K ≥8), the differences in SRI4 response rates were more pronounced and amounted to 24.5% and 33.6% between placebo and orelabrutinib groups. Trends were also observed for improvement of proteinuria, anti-dsDNA and IgG production, total B-cell count reduction, and complement increase (C4).

"In conclusion, orelabrutinib is generally safe and well-tolerated in patients with SLE, and preliminary results also suggest trending efficacy supporting further studies in larger and longer-term trials in SLE," Prof. Li closed.


Pregnancies in SLE: many complications for mothers and their unborn children

Pregnant women with systemic lupus erythematosus (SLE) have an increased risk of adverse pregnancy and neonatal outcomes, emphasising the need for specialised management of these patients. This was the main result of a retrospective study of over 50,000 women with SLE and delivery-related hospital admissions.

"As you all know, SLE affects women in their childbearing years," Prof. Bella Mehta (Weill Cornell Medical College, NY, USA) said in her introduction. In a previous study, she and her team found that in-hospital maternal and foetal mortality rates for women with SLE have declined over the past decades, but whether this is also true for morbidity is unclear [1]. To clarify this topic, Prof. Mehta performed a retrospective study using data on 40 million delivery-related admissions from a US database [2]. The researchers identified all delivery-related hospital admissions for patients with and without SLE from 2008 through 2017. Over 50,000 women had a diagnosis of SLE.

Patients with SLE were more likely to be older and had more comorbidities compared with non-SLE patients. Their risk of foetal morbidity was markedly elevated: 14.5% of the foetuses from SLE mothers were born prematurely compared with 7.3% in women without SLE (see Figure). Of the women with SLE, 8% of their foetuses had intrauterine growth restriction compared with 2.7% in women without SLE.

"Not only the babies but also the pregnant SLE women faced considerable health risks during the pregnancy. Compared with women without SLE, they were 4 times more likely to require a transfusion or develop a cerebrovascular disorder"
and 15 times more likely to develop acute renal failure. Other complications that were more frequent in pregnant women with SLE were eclampsia, disseminated intravascular coagulation, and cardiovascular and peripheral vascular disorders. Moreover, general medical issues like shock, sepsis, adult respiratory distress syndrome, and severe anaesthesia complications were more frequent in SLE patients compared with women without SLE.

Prof. Mehta pointed out that the database, unfortunately, did not include information on SLE disease activity, flares, the presence of nephritis, antiphospholipid or anti-Ro(SSA) antibodies, or medication use, which is a limitation of this study. “However, this work can help inform physicians to counsel and manage patients with SLE during pregnancy,” Prof. Mehta concluded.


**Lupus nephritis: Efficient treatment may reduce the risk of kidney disease advancement**

Progressing to advanced or end-stage chronic kidney disease (CKD) is not so rare in patients with systemic lupus erythematosus and lupus nephritis. The risk for these outcomes rises more than 2-fold in case of late or no remission after diagnosis of lupus nephritis or flares.

“Lupus nephritis affects up to 40% of patients with systemic lupus erythematosus and leads to end-stage CKD in about 17–33% of patients after 10 years. The prevalence of stage IV CKD is not known. However, these patients will develop end-stage CKD in about 2/3 of the cases after 6 years on average,” Prof. Konstantinos Tselios (McMaster University, Canada) laid the land on the background of his research [1].

The presented study investigated the potential influence of the timespan to remission as well as the occurrence of flares on the onset of advanced CKD. The study included 418 patients with confirmed lupus nephritis that were followed for at least 5 years.

After lupus nephritis diagnosis, remission was achieved by 50% within the first year and by 24.4% in the second and third years. Furthermore, 8.9% never reached remission, and 16.7% only did after 3 years. After a mean of 9.5 years, advanced CKD (eGFR ≤29 ml/min/1.73 m²) developed in 15.8% of patients. Baseline variables that were significantly different in patients who developed advanced CKD were: higher Systemic Lupus International Collaborating Clinics (SLICC) Damage Index, lower eGFR, higher prevalence of hypertension and proliferative nephritis, as well as more treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

“With regards to the variables of concern, patients who later developed advanced CKD needed more time from lupus nephritis to achieve complete remission, had significantly more flares within the first 5 years of disease, and received fewer immunosuppressive drugs compared with patients who had good outcomes,” Prof. Tselios stated.

A multivariate analysis identified circumstances that modified the risk of developing advanced CKD. Overall, results were best for patients who attained remission in the first year. In comparison with patients who achieved remission within 1 year, the risk of advanced CKD was significantly increased in those who had complete remission after 1-3 years (HR 2.48; 95% CI 1.2–5.4), no remission, or remission after 3 years (HR 2.99; 95% CI 1.4–6.3). Stratification according to <3 years or ≥3 years of immunosuppression was in favour of a longer time of therapy (P=0.0005). The occurrence of 1 flare was associated with a 2.7-fold increased risk for advanced CKD.

“In total, our findings emphasise the importance of early remission, as well as flare prevention with prolonged immunosuppressive treatment in order to maximise renal survival in lupus nephritis,” Prof. Tselios underlined.

1. Tselios K, et al. Impact of time to remission, flares, and exposure to immunosuppressives on the development of advanced chronic kidney disease (stage IV or worse) in lupus nephritis. POS0740, EULAR 2022 Congress, Copenhagen, 1–4 June, Copenhagen, Denmark.

**Antifibrotic therapy with nintedanib is beneficial for patients with negative prognostic factors**

A post-hoc analysis of the SENSCIS trial showed that treatment with nintedanib slows lung function decline in patients with negative prognostic factors. This supports the early use of antifibrotic therapy, particularly in patients with a high risk for loss of lung function.

In the phase 3 SENSCIS trial (NCT02597933), nintedanib reduced the rate of decline in forced vital capacity (FVC) over 52 weeks by 44% versus placebo in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD). “The SENSCIS trial reflected a real-world population and allowed
broad inclusion criteria,” Prof. Christopher Denton (University College London, United Kingdom) explained [1,2]. “Our analysis aimed to assess the effect of nintedanib on the rate of FVC decline but focusing on participants with risk factors for rapid FVC decline,” he said. The rate of decline in FVC over 52 weeks was analysed in participants with the following risk factors at baseline: early SSC (<18 months since the onset of first non-Raynaud symptom), elevated inflammatory markers (CRP ≥6 mg/L and/or platelets ≥330 x 10⁹/L), and significant skin fibrosis using 2 approaches: modified Rodnan skin score (mRSS) 15–40 or mRSS ≥ 18.

Compared with the total population of the SENSCIS trial, participants with 1 of these risk factors at baseline had a greater decline in lung function. “Conversely, once these patients are on nintedanib, there is a stabilisation,” Prof. Denton said. These results support the prompt initiation of nintedanib in patients with SSc-ILD to preserve lung function and improve patient outcomes.

“I think this is an important analysis in terms of our clinical practice and perhaps future trial designs. It does support using nintedanib in this group of patients that might be at particular risk for lung function decline,” Prof. Denton concluded.


Best of The Posters

Alarmingly low activity in patients with non-inflammatory and inflammatory rheumatic disease

A meta-analysis using fitness trackers to assess physical activity in patients with both non-inflammatory and inflammatory rheumatic diseases revealed that most patients fail the recommended number of daily steps. This is mostly not due to a lack of strength but rather a low motivation for physical efforts.

Wearable devices, such as fitness trackers, are an easy-to-use instrument to collect objective data related to physical activity, which is an important lifestyle factor for improving long-term health, especially in patients with rheumatic musculoskeletal disorders due to their increased cardiovascular risk. In the general population, wearable fitness trackers are increasingly popular to assess physical activity and get motivational cues.

A meta-analysis presented by Prof. Luca Quartuccio (University of Udine, Italy) aimed to evaluate wearable devices in patients with both non-inflammatory (i.e. fibromyalgia, osteoarthritis) and inflammatory (i.e. chronic inflammatory arthropathies, systemic autoimmune disorders) rheumatic diseases as a means to assess physical activity [1]. The researchers explored both daily steps and moderate-to-vigorous physical training as assessed with fitness trackers. The comparison of both parameters to reference values for healthy people was defined as a secondary outcome. According to a literature review, 7,000 daily steps were recommended [2]. The reference value for moderate-to-vigorous physical training was 150 min/week and was derived from WHO guidelines [3].

An overall of 51 studies, including 7,488 participants, were included. Participants reached the recommended threshold for moderate-to-vigorous physical training but failed the goal of 7,000 daily steps. Participants with rheumatic conditions reported 1092.6 fewer daily steps compared with the reference value. An even higher difference was reported in participants with autoimmune disease (1865.9 fewer steps) and osteoarthritis (1385.6 fewer steps), whereas patients with fibromyalgia and inflammatory arthropathies fared significantly better. Overall, younger people had a higher level of physical activity (6796.1 vs 5431.9 in the elderly).

The authors concluded that patients with rheumatic musculoskeletal diseases have an alarmingly low level of physical activity. The underlying diseases did not seem to impair strength but rather decrease tolerance or motivation.
for physical efforts. Wearable fitness trackers are an easy-to-use tool that should be integrated into future studies on physical activity. "The use of wearable devices may itself stimulate physical activity in patients with rheumatic musculoskeletal diseases," Prof. Quartuccio said.


High prevalence of fibromyalgia in patients with inflammatory bowel disease
An Italian study including patients with inflammatory bowel disease (IBD) revealed that those also suffering from fibromyalgia have a significantly impaired quality-of-life. IBD patients with this comorbidity present particularly psychological manifestations like depression, anxiety, and stress, but also chronic fatigue and sleep disturbances.

Fibromyalgia, characterised by widespread pain, fatigue, sleep disturbances, and functional symptoms, has a worldwide prevalence of 2–3% [1]. However, a meta-analysis published previously showed that the prevalence of fibromyalgia in the general population is significantly lower than in populations with certain diseases and can be as high as 12.9% in patients with IBD [1]. Information on the prevalence and the impact of fibromyalgia in patients with IBD is limited. To address this knowledge gap, Dr Laura Guida (Luigi Sacco University Hospital, Italy) and her team performed a study on consecutive patients attending 2 IBD hospital units from August to November 2021 [2]. Excluded were patients with severe disease activity (assessed by Crohn's disease activity index [CDAI] and Mayo score for ulcerative colitis [UC]) or those with other concomitant chronic diseases. Clinical and demographic data and patient-reported outcomes (PROs) were collected using the IBD Questionnaire (IBD-Q), Depression Anxiety Stress Scale-21 (DASS-21), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and Pittsburgh Sleep Quality Index (PSQI). An expert rheumatologist diagnosed fibromyalgia according to the 2011 ACR classification criteria.

Among the 196 IBD patients enrolled in the study, 105 (53.6%) had Crohn's disease (CD), and the rest had UC. The overall prevalence of fibromyalgia in the IBD cohort was 8.7%, with 7.6% in the CD group and 9.9% in the UC group. As expected, the prevalence was higher in women (11.6%) than in men (6.3%). No significant demographic (i.e. gender, age) or clinical (i.e. body mass index, C-reactive protein, disease activity, ongoing treatment modality) differences were found between the groups with and without fibromyalgia as comorbidity.

As assessed by IBD-Q, the quality-of-life in IBD patients with fibromyalgia was significantly lower than in those who did not have fibromyalgia (P<0.001). Furthermore, they experienced significantly worse symptoms (i.e. depression, anxiety, stress, chronic fatigue, and discomfort) than patients without fibromyalgia (P<0.001; see Table).

Table: High prevalence of depression, anxiety, and stress in patients with inflammatory bowel disease and fibromyalgia [1]

<table>
<thead>
<tr>
<th></th>
<th>IBD</th>
<th>IBD+FM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>179</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>IBD-Q</td>
<td>176.9</td>
<td>150.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DASS-21 Depression</td>
<td>8.24</td>
<td>15.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DASS-21 Anxiety</td>
<td>9.13</td>
<td>16.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DASS-21 Stress</td>
<td>6.13</td>
<td>13.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FACIT-F</td>
<td>38.2</td>
<td>25.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IES-R</td>
<td>16.3</td>
<td>36.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

IBD, inflammatory bowel disease; FM, fibromyalgia; IBD-Q, inflammatory bowel disease Questionnaire; DASS-21, Depression Anxiety Stress Scale-21; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; IES-R, Impact of Event Scale-Revised.

Moreover, multivariate analysis showed that disease activity (CDAI; P=0.025), chronic fatigue (FACIT-F; P=0.006), and sleep disturbances (PSQI; P=0.044) have a significant influence on the quality-of-life of CD patients. In contrast, disease severity (Mayo score; P=0.012) was the only independent variable that positively correlated with quality-of-life in UC patients.

In conclusion, Dr Guida emphasised that the presence of fibromyalgia in IBD can considerably impact the quality-of-life, especially by causing depression, anxiety, stress, chronic fatigue, sleep disturbances, and discomfort.