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PEER-REVIEWED CONFERENCE REPORT

Dazodalibep benefits Sjögren's syndrome

A novel non-antibody fusion protein led to a significantly lower symptom burden in patients with Sjögren's syndrome with unacceptably high symptom burden.

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Cardiovascular safety of JAK inhibitors?

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Comparing the increase in bone mineral density after 1 year of treatment with romosozumab versus denosumab, the adjusted rates were significantly higher in favour of the romosozumab arm.

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Letter from the Editor

Dear colleagues,

Milan is a city that sets the blood racing with its "3Fs", from fashion to Formula 1 racing to football. The football excitement was palpable in early June 2023 when the "Nerazzurri", better known as Inter Milan, prepared to participate in the Champions League final. Alas, Inter lost, and the fans will be keen to forget and move on. Not so for the EULAR attendees, who congregated in the city between the 30th of May and the 3rd of June and were treated to a real fest of full-throttle clinical and translational Rheumatology with over 12,000 attendees at the MiCo Convention Center. The post-COVID crowd moving between various activities slowed movements from place to place, but a high quality of research activity will linger long in the collective minds.

In this report, we select a small fraction of the excellent abstracts to give a snapshot of new and emerging insights in Rheumatology, including data on the major inflammatory arthropathies and autoimmune connective tissue diseases. We also select studies concerning new therapy strategies in osteoarthritis and novel approaches to gout. We genuinely believe that the reader will find these topics of considerable value and interest and will be impressed with the research activity across a wide front in Rheumatology.

My impression was that the congress attendees were delighted to return to the pre-COVID format with lots of opportunities for direct interactions over the recent more restrictive contacts due to the COVID-19 pandemic. Thankfully, this is now receding in the rear-view mirror as we accelerate away and take the scenic route across the Alps towards Vienna, where EULAR 2024 congress awaits.

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Sincerely,

Prof. Dennis McGonagle

Biography

Dennis McGonagle, FRCPI, PhD, is an Academic Rheumatologist at the University of Leeds and section head of Experimental Rheumatology. He graduated in Medicine from the University College Dublin in 1990 and undertook postgraduate training in Dublin and Leeds where he completed his PhD. He has developed the modern enthesitis model for spondyloarthropathies and psoriatic arthritis including the cytokine mediated enthesis originating theory of disease (Lancet 1998). He also described the synovioentheseal complex, nail anchorage to the skeleton, developed an integrated biomechanical and immunology model for PsA, and a mechanistic disease classification of immune diseases (PLoS Med 2006). His group also discovered synovial fluid mesenchymal stem cells, which is being researched towards osteoarthritis therapy development. Prof. McGonagle has also served on the EULAR scientific committee and is a member of the Editorial Board of ARD.

Conflict of Interest Statement:
Prof. McGonagle has undertaken research and/or educational programme activities with Pfizer, MSD, AbbVie, BMS, UCB, Novartis, Celgene, and J&J.

Late-breaking Oral Abstracts

Selective JAK1/TYK 2 inhibitor effective in patients with difficult-to-treat RA

In a Chinese trial, a novel JAK1/TYK2 inhibitor was able to achieve remission in >30% of participants with difficult-to-treat rheumatoid arthritis (RA). Its activity might be explained by blocking multiple pro-inflammatory cytokines that signal via JAK1 and TYK2.

According to the EULAR definition, patients with RA who failed ≥2 biological disease-modifying antirheumatic drugs (DMARDs)/targeted synthetic DMARDs (with different mechanisms of action) after failing conventional synthetic DMARD therapy (unless contraindicated) can be considered "difficult-to-treat" [1]. The definition also implies that these patients remain with active or symptomatic disease and that the management of signs or symptoms is perceived as problematic. According to this definition, 5-20% of RA patients fulfil these criteria [2].

As Prof. Xiaofeng Zeng (Peking Union Medical College Hospital, China) pointed out, not many treatment options are available for difficult-to-treat patients with RA. Both cytokines signalled by JAK1 and those regulated by TYK2, including IL-17 and IL-23, are involved in RA pathogenesis. This was the rationale for finding out whether TLL-018, an investigative, dual JAK1/TYK2 inhibitor, can overcome resistance to JAK1-selective inhibitors [3].

A total of 101 participants with moderate-to-severe active RA and inadequate response or intolerance to methotrexate were randomised to receive tofacitinib 5 mg daily or TLL-018 in different dose regimens (10 mg, 20 mg, or 30 mg). The primary study endpoint was the percentage of participants who achieved ACR50 at week 12. In addition, the percentages of participants who achieved ACR20, ACR70, and remission (disease activity score [DAS]28 ≤2.6) were assessed as secondary endpoints.

At week 12, 65.4% of participants treated with TLL-018 20 mg and 72% of those treated with TLL-018 30 mg achieved ACR50 compared with 41.7% of participants treated with tofacitinib ($P<0.05$ for both comparisons). In addition, the agent was also superior to placebo in secondary endpoints. Thus, "17% of participants treated with tofacitinib compared with >30% treated with the new compound achieved remission," Prof. Zeng commented. TLL-018 in the 2 highest doses achieved an ACR50 response of >66%, independent of previous treatment (methotrexate only, prior biological drug, or prior TYK inhibitor).

The drug was also relatively well tolerated, with the most frequently reported adverse events being infections, in particular herpes zoster, elevations of gamma-glutamyltransferase, and hypertriglyceridemia. "Interestingly, the middle dose group had more adverse events than the high dose groups," Prof. Zeng said. Lipid changes occurred in the first 4 weeks and then stabilised. Whilst we have previously seen studies in RA that use a biological DMARD as a reference arm, this use of tofacitinib as a JAK inhibitor comparator arm is noteworthy.

Prof. Zeng concluded that TLL-018 20 mg can overcome resistance to tofacitinib and, therefore, may be a valuable treatment option for difficult-to-treat RA.

1. Nagy G, et al. Ann Rheum Dis. 2021;80:31-5.
2. Watanabe R, et al. Front Med (Lausanne). 2022;9:1049875.
3. Zeng X, et al. Head-to-Head Comparison of TLL-018 and Tofacitinib in Patients with Active Rheumatoid Arthritis: Interim Results from a Phase IIa Study. LB0001, EULAR 2023, 31 May–3 June, Milan, Italy.

Novel 2-drug combo improves treatment possibilities for patients with refractory gout

Almost half of the participants with refractory gout achieved serum uric acid levels <6 mg/dL with a novel uricase-based therapy in the DISSOLVE I and DISSOLVE II trials. The common problem of anti-drug antibody (ADA) formation was solved by a second immune-tolerising component applied 30 minutes prior to uricase.

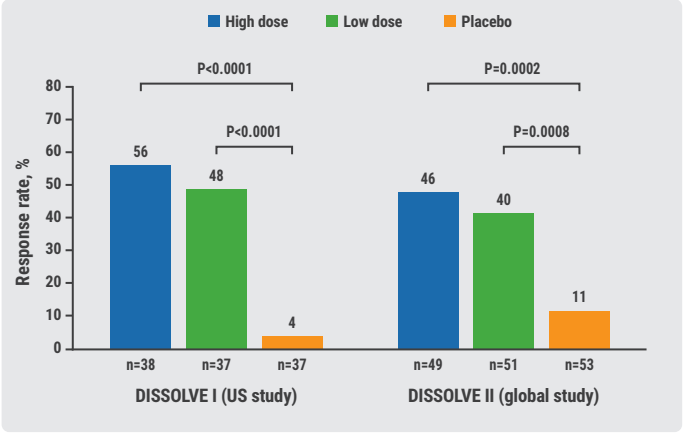
Uricase-based therapy is recommended for gout patients who have failed to achieve uric acid-lowering targets, but ADA diminish their effectiveness, leading to treatment failure rates in up to 38% of cases [1,2]. "Pegadricase is a potent pegylated uricase that converts uric acid to soluble and readily excreted allantoin," Prof. Herbert SB Baraf (Center for Rheumatology and Bone Research, IL, USA) explained the mode of action of 1 component during the presentation [3]. However, as most

uricases, it also elicits a vigorous ADA response, limiting its use as a monotherapy. Therefore, SEL-110, the second component of the novel infusion therapy, is administered 30 minutes before pegadricase. SEL-110 is an immune-tolerising nano-encapsulated rapamycin that has demonstrated dose-dependent inhibition of anti-pegadricase antibodies in previous trials.

In the phase 3 studies DISSOLVE I (NCT04513366) and DISSOLVE II (NCT04596540), participants were enrolled if they had ≥3 gout flares within 18 months before screening, ≥1 tophus, or a current diagnosis of gouty arthritis and failed to normalise serum uric acid and control symptoms with any xanthine oxidase inhibitor. They were randomised to receive a high or a low dose of the novel 2-drug combo SEL-212 or placebo, every 28 days for a total of 6 treatments. The primary endpoint was the percentage of participants achieving serum uric acid levels <6 mg/dL for at least 80% of the sixth 28-day treatment period. "Stringent stopping rules were implemented to minimise the risk of infusion-related adverse events," Prof. Baraf emphasised.

Included were 265 participants whose demographic characteristics were balanced for age, BMI, and sex, but racial imbalances existed in both studies. Gout severity was numerically greater in the 153 participants included in DISSOLVE II. The primary efficacy endpoint was met for both studies and doses (see Figure). In the DISSOLVE I study, 58% of participants in the high-dose group (n=38) and 48% in the low-dose group (n=37) responded to treatment (both P<0.0001 vs placebo). The corresponding numbers in the DISSOLVE II study were 46% in the high-dose group (P=0.0002 vs placebo) and 40% in the low-dose group (P=0.0008 vs placebo). Median

Figure: Primary trial endpoint: response to SEL-212 versus placebo at week 12 [3]



change in serum uric acid levels indicates large reductions in at least half of the participants. Participants older than 50 years had similar response rates.

Treatment was relatively tolerable. The infusion reaction incidence was 3.4% in the high-dose group.

Prof. Baraf concluded that SEL-212 might potentially provide a new once-monthly uricase-based treatment option for patients with refractory gout.

1. Fitzgerald JD, et al. Arthritis Care Res (Hoboken). 2020;72:744-60.
2. Botson J, et al. Arthritis Rheumatol. 2023;75:293-304.
3. Baraf HSB, et al. Safety and efficacy of SEL-212 in patients with gout refractory to conventional treatment: outcomes from two randomised, double-blind, placebo-controlled, multicenter phase III studies. LB0002, EULAR 2023, 31 May–3 June, Milan, Italy.

Dazodalibep improves dryness, fatigue, and pain in patients with Sjögren's syndrome with a high symptom burden

A novel non-antibody fusion protein led to a significantly lower symptom burden in patients with Sjögren's syndrome with an unacceptable high symptom burden and limited extraglandular organ involvement. Of note, these patients are rarely included in clinical trials.

Sjögren's is a systemic auto-immune disease generally driven by the cardinal symptoms of dryness, pain, and fatigue [1,2]. A substantial part of patients with Sjögren's syndrome suffers from an unacceptable symptomatic burden (equalling a score in the EULAR Sjögren's Syndrome Patient Reported Index [ESSPRI] ≥5) and limited extraglandular organ involvement. The ESSPRI focuses on the symptoms of dryness, fatigue, and pain. Moreover, these participants have largely been excluded from recent therapeutic trials, which only enrolled subjects with moderate-to-high systemic disease activity.

Dazodalibep is a novel non-antibody fusion protein that acts as an antagonist of CD40L. Thus, it inhibits the costimulatory signals between immune cells, including T cells, B cells, and antigen-presenting cells. The drug was assessed in the randomised, double-blind, placebo-controlled, parallel-arm study ALISS (NCT04129164) in 2 different adult populations with Sjögren's syndrome. At the EULAR meeting, Dr Chiara Baldini (University of Pisa, Italy) presented the study results of population 2 (n=109), defined as those participants with an unacceptable symptom burden and limited systemic disease activity [3].

Participants were randomised 1:1 to placebo or dazodalibep, and 102 completed the study. At day 169, a statistically significant higher change in ESSPRI total score (primary study endpoint) in participants treated with dazodalibep was seen, compared with placebo (-1.80 with dazodalibep vs -0.53 with placebo; P=0.0002). Similar results were observed for the 3 individual domains of ESSPRI (dryness, fatigue, and pain). "The study was not powered for secondary outcomes, but despite this, we saw a significant reduction in the fatigue score and a numerical decrease in other secondary outpoints," Dr Baldini said.

The drug was also relatively well tolerated, with the most frequently reported adverse events occurring in ≥5% of treated subjects, being COVID-19, nasopharyngitis, anaemia, and diarrhoea.

Larger clinical trials are now warranted to confirm the clinical efficacy and safety of dazodalibep in this subgroup of patients with Sjögren's syndrome.

1. Bowman SJ, et al. Rheumatology (Oxford). 2004;43:758-64.
2. Bowman SJ, et al. J Rheumatol. 2003;30:1259-66.
3. St. Clair EW, et al. Dazodalibep in Sjogren's subjects with an unacceptable symptom burden: safety and efficacy from a phase 2, randomized, double-blind study. LB0003, EULAR 2023, 31 May–3 June, Milan, Italy.

COVID-19: Young adults with auto-immune diseases have different risks than their healthy counterparts

Having a diagnosis of rheumatic and musculoskeletal diseases (RMDs) entailed a higher chance of SARS-CoV-2 infection in comparison with healthy controls (HC). Also, young adults with RMDs and non-rheumatic auto-immune disease (nrAD) were significantly more prone to early mild adverse events (AE) after 1 or 2 vaccine doses than HC.

Dr Alessia Alunno (University of L'Aquila, Italy) pointed out that young adults with a chronic inflammatory disease, mainly those diagnosed at paediatric age, have long exposure to inflammation and immunosuppressive treatments, despite their younger age [1]. As for research on COVID-19, studies focusing on this population are currently lacking. "We tried to fill this knowledge gap," Dr Alunno explained, presenting results that evaluated COVID-19 severity, breakthrough infections, vaccine-related AE, and post-vaccine flares in patients aged 18 to 35. Data pertaining to the years 2021 and 2022 was collected from the international COVID-19 Vaccination in Autoimmune Diseases (COVAD) 1 and 2 questionnaires.

Included were 6,010 responders, among them 1,692 with RMDs, 400 nrAD, and 3,918 HC. The disease groups cohort consisted mainly of women at a rate of over 80%, while the proportion was lower in the HC (64%). At least 2 vaccine doses were administered to 75–83% of the cohort. The disease duration was around 7 years. "We observed that over 90% of patients with RMDs and only 20% with nrAD were exposed to immunosuppressants before vaccination," Dr Alunno described.

Overall, 24–28% of the study cohort ever tested positive for SARS-CoV-2 infection. The infections were nearly always symptomatic, but hospitalisation, supplemental oxygen, or intensive care admission were rarely necessary. Looking at the likelihood of being infected pre- or post-vaccination, the results among the groups differed. Pre-vaccine infections were less frequent in patients with RMDs versus HC (OR 0.6; 95% CI 0.4–0.9) but similar in nrAD compared with HC. "This can be easily attributed to the straight shielding in people receiving immunosuppressants in the early phases of the pandemic," Dr Alunno commented. In contrast, after vaccination, patients with RMDs were nearly 3 times more likely to be infected than HC (OR 2.7; 95% CI 2.1–3.5).

In terms of clinical manifestations, RMDs patients were more prone to arthralgia than HC, independent of the time of infection. Flares were self-reported post-infection by 5% (RMDs) and 1.5% (nrAD) and post-vaccination by 10% and 7%, respectively. Of note, only 41% (RMDs) and 27% (nrAD) of these prompted a change in dose or type of medication.

The likelihood for early mild AE after 1 or 2 vaccine doses was about twice as high for both disease groups compared with HC (OR 2.4; 95% CI 2.0–3.1 for RMDs and OR 2.0; 95% CI 1.4–2.9 for nrAD). Differences between groups for late, mild, or severe AE were not significant after any number of vaccine doses.

1. Alunno A, et al. COVID-19 severity, breakthrough infections and anti-SARS-COV-2 vaccine safety in young people with rheumatic and non-rheumatic autoimmune diseases: results from the COVAD1 and COVAD2 projects. LB0006, EULAR 2023, 31 May–3 June, Milan, Italy.

RA in 2023

Poly-refractory RA: not common, but still present

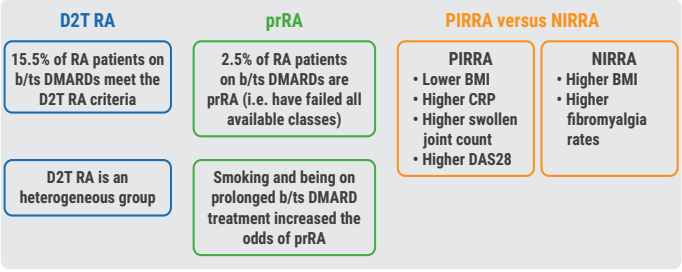
Patients with difficult-to-treat (D2T) rheumatoid arthritis (RA) represented 15.5% of a Leeds' study cohort, whereas poly-refractory (pr)RA was found in 2.5%. Duration of >9.5 years of treatment with biologic/targeted synthetic (b/ts) disease-modifying antirheumatic drugs (DMARDs) and smoking significantly increased the odds of prRA.

Although current RA management possibilities entail fewer disease complications and better control of the inflammatory processes than before, D2T RA and prRA still pose a challenge in the medical treatment of those affected [1]. In 2021, EULAR defined criteria for D2T RA [2]. "In summary, it is the failure of at least 2 different types of b/ts DMARDs after failing conventional DMARDs in the presence of active or progressive disease," Dr Paula David (University of Leeds, UK) informed [1]. By this broad definition, D2T RA applies to a very heterogeneous group of patients. The presented cross-sectional, single-centre study aimed not only to investigate the prevalence of D2T RA and prRA, but also to further characterise possible distinctive profiles according to the presence of disease activity on ultrasound.

Out of 1,591 reviewed medical records, 247 (15.5%) fulfilled the EULAR criteria of D2T RA. Among these, 40 patients were prRA, meaning they had failed all available b/ts DMARD classes. The demographic and clinical profiles of the 207 remaining D2T RA patients and those of prRA were largely similar. However, disease duration and time since first b/ts DMARD were significantly longer in the prRA group (P=0.008 and P=0.001, respectively). Also, the proportion of smoking differed significantly between both groups (4% [D2T RA] vs 20% [prRA], P=0.002). Significant differences between the 2 groups were also detected with a higher Disease Activity Score in 28 joints (DAS28), median C-reactive protein (CRP), and rate of patients with elevated CRP. A multivariate logistic regression identified 3 factors that were significantly associated with prRA. Exposure to b/ts DMARDS >9.5 years (OR 7.45; 95% CI 1.88–29.5) and especially smoking (OR 9.86; 95% CI 1.44–67.4) increased the likelihood of prRA. "We found that the steroid use in the past year reduced the probability of being classified as prRA," Dr David further stated.

Within 107 patients with information on a recent ultrasound, the investigators compared 2 different subgroups of D2T RA, both presenting a DAS28-CRP of ≥3.2: patients with persistent inflammatory refractory RA (PIRRA) had ultrasound-detected synovitis in at least 1 swollen joint, and in non-inflammatory refractory RA (NIRRA), the ultrasound-detected synovitis was absent in suspected clinically involved joints. "When comparing the PIRRA and NIRRA, we found that they also have very similar profiles, but the NIRRA group had higher BMI, obesity, and higher rates of fibromyalgia," Dr David said. On the other hand, e.g. the swollen joint count, DAS28, and elevated CRP were higher in the PIRRA group. A swollen joint count >2 was associated with higher odds of PIRRA (OR 5.19; P<0.001), while each unit of higher BMI reduced the probability of PIRRA (OR 0.89; P<0.01). The figure summarises these study results (see Figure).

Figure: Poly-refractory RA: study findings in summary [1]



D2T, difficult-to-treat; RA, rheumatoid arthritis; prRA, poly-refractory RA; PIRRA, persistent inflammatory refractory RA; NIRRA, non-inflammatory refractory RA; b/ts DMARD, biologic/targeted synthetic disease-modifying antirheumatic drug; BMI, body mass index; CRP, C-reactive protein; DAS28, Disease Activity Score in 28 joints.

In her conclusion, Dr David underlined that it remains to be determined whether PIRRA patients benefit more from b/ts DMARD switching than NIRRA patients.

1. David P. Real world "poly-refractory RA": a rare but unmet clinical challenge. OP0134, EULAR 2023, 31 May–3 June, Milan, Italy.
2. Nagy G, et al. Ann Rheum Dis. 2021;80:31-5.

COBRA-Slim bio-induction: no benefit compared with the standard regimen

The CareRA2020 study did not find a significant difference in the long-term effectiveness of COBRA-Slim bio-induction (addition of etanercept) compared with the standard COBRA-Slim regimen (addition of leflunomide) in initial insufficient responders in participants with

early rheumatoid arthritis (RA). However, the bio-induction group showed a higher rate of participants on methotrexate monotherapy and a lower requirement for biological or targeted disease-modifying antirheumatic drugs (DMARDs).

The management of early RA is crucial to prevent long-term joint damage and to improve patient outcomes. The EULAR recommends a combination of methotrexate and short-term glucocorticoids as the first-line treatment for early RA. However, there is ongoing research to explore alternative approaches that offer a better balance between efficacy, safety, and cost-effectiveness.

The Care in Early RA 2020 (CareRA2020) trial was conducted to determine the long-term effectiveness of 2 treatment strategies in participants who had an insufficient response to the initial COBRA-Slim induction therapy, which consisted of methotrexate and step-down prednisone [1]. The trial compared the outcomes of adding a second conventional DMARD, leflunomide, with the outcomes of using a temporary course of etanercept, a biological DMARD.

Participants were classified as insufficient responders if they did not achieve the target 28-joint Disease Activity Score using C-reactive protein (DAS28-CRP) with the induction regimen. Insufficient responders were randomised into 2 groups: 1 group received the standard COBRA-Slim treatment with the addition of leflunomide 10 mg/day, while the other group received COBRA-Slim bio-induction with the addition of etanercept 50 mg/week for 24 weeks. The primary outcome was the difference in DAS28-CRP over time.

Both treatment groups had comparable DAS28-CRP scores over 104 weeks, indicating no superiority of COBRA-Slim bio-induction therapy compared with the standard COBRA-Slim regimen (ß 0.061; 95% CI -0.172 to 0.294; P=0.609). However, at the end of the trial, a higher proportion of participants in the bio-induction group were treated with methotrexate monotherapy, while fewer required biological or targeted synthetic DMARDs.

According to the authors, further investigation is needed to assess the potential advantages of incorporating temporary biological DMARDs earlier in the treat-to-target approach.

1. Bertrand D, et al. Effectiveness of COBRA-Slim with or without early access to a temporary 6-month course of etanercept in early RA: Primary outcome of the 2-year, pragmatic, randomized CareRA2020 trial. OP0129, EULAR 2023, 31 May–3 June, Milan, Italy.

AI almost as successful as experts in predicting early RA

After a training period, a novel deep-learning artificial intelligence (AI) system was almost as accurate as an expert using the RAMRIS scoring system in interpreting MRI scans of wrists and feet to predict early rheumatoid arthritis (RA). AI-based systems might even perform better after feeding them more clinical data.

In many patients, clinically suspect arthralgia (CSA) progresses to early onset arthritis, RA, or other arthritides. Predicting early RA from MRI images can help initiate prompt treatment, possibly preventing the chronicity of the disease. Until present, visual scoring (e.g. with the RAMRIS scoring system) from extremity MRI scans is used to manually identify key risk factors for the chance of developing RA. The study group of Dr Yanli Li (Leiden University Center, the Netherlands) assessed whether AI interpretations of MRI images could provide more accurate predictions than visual scoring by medical staff [1].

The model was first trained to understand anatomy from MRIs of wrists and metacarpophalangeal joints of healthy controls. In a second step, it learnt to distinguish between the different groups (patients with CSA vs healthy controls and early-onset arthritis vs healthy controls). In a third step, the AI was taught to distinguish RA from other arthritides. Finally, the system had to predict RA development in 2 years in patients with CSA. The model's accuracy was evaluated with the area under the receiver operator curve (AUC).

The AI analysed MRI scans from 1,974 people with either early-onset arthritis (n=1,247) or CSA (n=727), of whom 651 went on to develop RA.

On the test set, the proposed model obtained a mean AUC of 0.683 in the early-onset arthritis group and 0.727 in the CSA group. These accuracies are close to the expert levels using RAMRIS.

As Dr Li emphasised, the system can be further improved with more clinical data. Moreover, the self-learning AI system showed similar efficacy for scans of either wrists or feet. As Dr Li explained during the presentation, AI-based RA prediction is reliable as it looks at known inflammatory signs and features such as synovial inflammation.

1. Li Y, et al. Exploring the Use of Artificial Intelligence in Predicting Rheumatoid Arthritis, Based on Extremity MR Scans in Early Arthritis and Clinically Suspect Arthralgia Patients. OP0002, EULAR 2023, 31 May–3 June, Milan, Italy.

Worse self-management in patients with inflammatory arthritis in the presence of comorbid anxiety or depression

A high prevalence of mental health issues was found in Danish registry data that investigated patients with inflammatory arthritis. The presence of anxiety or depression was associated with a higher likelihood of self-management impairment.

"Little is known on the mental health in patients with inflammatory arthritis," Ms Sofie Bech Vestergaard (Aarhus University Hospital, Denmark) informed [1]. This is why the Danish cross-sectional study focused on the possible effect of anxiety and depression on self-management behaviour in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and spondylarthritis (SpA). "We know that poor mental health is associated with overall poor health, that is why it is such an important area," Prof. Jette Primdahl (IRS Danish Hospital for Rheumatic Diseases, Denmark) underlined in her comment on the study [2].

Over 12,000 patients identified from the Danish Rheumatology database and National Patient Registry completed an electronic questionnaire [1]. Patients had a mean age of 62 and a disease duration of 12 years. Women represented 63.4% of the study population. Possible anxiety and depression were both defined by a score between 8 and 10 on the Hospital Anxiety and Depression Scale (HADS), while a score of ≥11 was used for definite cases.

The prevalence of anxiety varied among the different groups: 34.5% in SpA, 32.1% in PsA, and 22.1% in RA. Depression was present in somewhat similar proportions, with a prevalence of 27.2% in PsA, 26.4% in SpA, and 18.6% in RA. Being a woman, having basic education, being under 55 years, or being recently diagnosed (less than 3 years) was associated with a higher prevalence of anxiety and depression.

"Patients with clinical levels of anxiety and depression symptoms were more likely to have low levels of self-management behaviour for all included measures," Ms Vestergaard revealed. Thus, treatment adherence, patient activation in healthcare, and physical activity were significantly lower in those suffering from anxiety or depression. Moreover, Ms Vestergaard highlighted that patients with definite depression had marked difficulties handling new situations concerning their health condition, compared with patients without depression (OR 7.09; 95% CI 6.11–8.22). "We need a systematic approach to identify those patients who suffer from anxiety and depression and refer them appropriately. We may need to develop new interventions to dedicate to these patients," Prof. Primdahl advocated in light of these results [2].

1. Vestergaard SB, et al. Self-management behaviour, anxiety and depression in patients with inflammatory arthritis – a cross-sectional nationwide study among >12,000 Danish patients. OP0176, EULAR 2023, 31 May–3 June, Milan, Italy.
2. Primdahl J. Press conference, EULAR 2023, 31 May–3 June, Milan, Italy.

Disease activity-guided dose reduction may be a long-term option for stable RA

No negative impact on radiographic progression was found when the treatment dosages of RA patients on biologic/targeted synthetic (b/ts) DMARDs were decreased according to a treat-to-target strategy. Up to year 10, disease activity-guided medication of these patients resulted in a reduction of the defined daily dose (DDD) of more than 50%.

The DRESS study (Dutch Trial Register, NTR 3216) and its extension up to year 3 determined that disease activity-guided dose optimisation in at least 6 months stable RA patients can be successful, safe, and cost-effective [1,2]. With the goal of gaining insights into the long-term viability of this strategy, the study cohort was observed further up to year 10 using data from their electronic health records [1]. The mean time-weighted disease activity was measured by the 28-joint Disease Activity Score using C-reactive protein (DAS28-CRP). "It is important to measure disease activity and set a goal, using, e.g. DAS28 criterion, as well as to increase the dose when the disease activity increases above a certain threshold," Dr Noortje van Herwaarden (Sint Maartenskliniek, the Netherlands) underlined.

Most of the 170 patients in the study cohort were women (64%), the mean age was 59, and RA was present at an average of 10 years. About 60% already had erosive disease at baseline. "Disease activity remained low throughout the years," Dr van Herwaarden indicated, referring to a DAS28-CRP of just over 2. The TNF inhibitors doses decreased from the baseline 97% of the DDD to 49% at year 5, and to 51% at year 10. Looking at all b/ts DMARDs, the respective percentage of the DDD was 97% (year 0) and 56% (years 5 and 10). At a median, patients had 2 attempts of dose optimisation, and in 74% of cases, a tapering to full discontinuation was achieved. The first failed discontinuation attempt lasted a median of 7 months, and

there was a median of 6.8-year drug survival after restarting medication or increasing dosage.

Additionally, "radiographic progression exceeding the smallest detectable change was associated independently with disease activity, but not with b/ts DMARD dose," Dr van Herwaarden stated. "Good quality treat-to-target is important to mitigate radiographic joint damage," she emphasised.

In conclusion, these findings suggest that disease activity-guided dose optimisation yields stable low disease activity over time.

1. Van Herwaarden N, et al. Disease activity-guided dose optimisation including discontinuation of TNF-inhibitors in rheumatoid arthritis is effective for up to 10 years: results of the DRESS study. OP0131, EULAR 2023, 31 May–3 June, Milan, Italy.
2. Bouman CA, et al. Ann Rheum Dis. 2017;76:1716-22.

Cardiovascular safety of JAK inhibitors: reassuring results from a real-world study

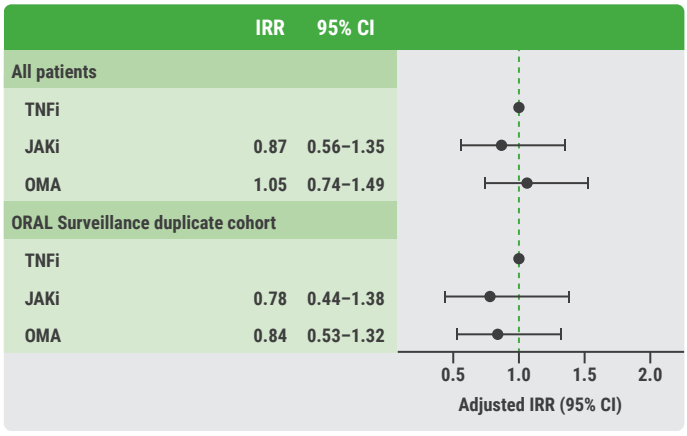
The incidence of major adverse cardiovascular events (MACE) with the use of JAK inhibitors (JAKi) in registries was not higher compared to therapy with TNF inhibitors (TNFi) in patients with rheumatoid arthritis (RA). Moreover, the risk was not elevated in the subgroup of patients with cardiovascular (CV) risk factors.

The objective of the "JAK-pot" study presented by statistician Mr Romain Aymon (Geneva University Hospital, Switzerland) was to assess the incidence of MACE in RA patients treated with JAKi, compared with biologic agents in a large, multi-country, real-world population [1]. "With our subgroup analysis, we wanted to replicate the main inclusion criteria of the ORAL Surveillance study", Mr Aymon explained. In the post-authorisation safety trial ORAL Surveillance (NCT02092467), an increased risk of MACE and venous thromboembolism was found during therapy with tofacitinib versus TNFi in patients with RA and at least 1 additional CV risk factor [2]. It led to issued warnings from both European and US authorities, which raised concern about the safety of JAKi.

The data of the "JAK-pot" study was derived from 14 registries from an international collaboration. Patients starting JAKi, TNFi, or biological DMARDs with other modes of action (OMA, namely abatacept, rituximab, sarilumab, or tocilizumab) were included. A sub-analysis was performed on patients of at least 50 years old and with 1 or more CV risk factors, mimicking the ORAL Surveillance inclusion criteria. The exposure period was from treatment initiation until the first of either: 3 months after discontinuation, start of a new treatment, end of participation in the register, or end of the study period.

Across the 50,325 treatment initiations considered, 182 incident MACE were reported. The study did not find a significantly higher risk of MACE in RA patients treated with JAKi compared with TNFi. "The crude incidence rates for JAKi were lower than for TNFi," Mr Aymon said. However, the adjusted regression analysis demonstrated no significant difference in the incidence of MACE between JAKi versus TNFi (IRR 0.87; 95% CI 0.56–1.35) and OMA versus TNFi (IRR 1.05; 95% CI 0.74–1.49; see Figure).

Figure: Adjusted IRR for MACE according to treatments in the "JAK-pot" study [1].



TNFi, TNF inhibitors; JAKi, JAK inhibitors; OMA, DMARDs with other modes of action; IRR, incidence rate ratio; CI, confidence interval.

The ORAL Surveillance duplicate cohort accounted for 38.4% of treatment courses and had a higher incidence of MACE in each treatment group. But, similarly to the overall population, there was no significant difference in the incidence rates of MACE observed between JAKi versus TNFi (IRR 0.78; 95% CI 0.44–1.38) and OMA versus TNFi (IRR 0.84; 95% CI 0.53–1.32). "There were no differences in any outcomes, only maybe a small venous thromboembolic event signal in the ORAL Surveillance duplicate cohort," Mr Aymon concluded.

1. Aymon R, et al. Incidence of major adverse cardiovascular events in patients with rheumatoid arthritis treated with JAK-inhibitors compared to bDMARDs: data from an international collaboration of registries (the "JAK-pot" study). OP0219, EULAR 2023, 31 May–3 June, Milan, Italy.
2. Ytterberg SR, et al. N Engl J Med. 2022;386:316-26.

Spondylarthropathies: New Developments

AxSpA: Adalimumab biosimilar equally effective as IL-17 inhibitor in hindering radiographic progression

Radiographic progression in patients with axial spondyloarthritis (axSpA) was equally controlled by the IL-17A inhibitor secukinumab in comparison with the anti-TNF adalimumab biosimilar SDZ-ADL. At week 104, the efficacy of both treatment options was demonstrated by an overall low change from baseline in modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS).

"We report the very first head-to-head study in axSpA comparing secukinumab and adalimumab biosimilar with the aim of measuring any differences in radiographic progression," Prof. Xenofon Baraliakos (Rheumazentrum Ruhrgebiet, Germany) announced [1]. The 2-year, phase 3b SURPASS study (NCT03259074) enrolled 859 biologic-naïve patients with active radiographic axSpA and a high risk of radiographic progress, with high-sensitivity C-reactive protein (hsCRP) ≥5 mg/L and/or the presence of at least 1 spinal syndesmophyte. The trial design foresaw 3 groups, receiving either adalimumab biosimilar SDZ-ADL 40 mg or secukinumab at 150 mg or 300 mg dosages as study treatment. The primary endpoint was defined as the proportion of participants without radiographic progression at week 104, measured by an mSASSS change from baseline ≤0.5 in the assessment of 3 different central readers.

Baseline demographics showed a mean age of 42.1, and 78.5% of the participants were men. The mean mSASSS was 16.6, the mean hsCRP was 20.4 mg/L, and 73% had ≥1 syndesmophyte. The results revealed similar and non-significant results for the primary endpoint across all groups, with rates of 66.1% (secukinumab 150 mg), 66.9% (secukinumab 300 mg), and 65.9% (SDZ-ADL) of participants not developing radiographic progression up to week 104. Additionally, respective mean values for change from baseline in mSASSS were low, at 0.54, 0.55, and 0.72, respectively, a fact that Prof. Baraliakos highlighted as an important message. In line with these results, the rates of participants without new syndesmophytes after 2 years ranged between 53.3% and 56.9%, without significant inter-group differences. The analysis furthermore did not find relevant dissimilarities in the reduction of oedema scores for the spine and sacroiliac joint.

"We did not observe any new safety signals; overall, about 80% of the participants had at least 1 adverse event, the most frequent being nasopharyngitis," Prof. Baraliakos stated. For some specific adverse events, the exposure-adjusted incidence rates (EAIR) of secukinumab versus SDZ-ADL differed, among them Crohn's disease (EAIR 1.0 vs 0.2) and uveitis (EAIR 2.1 vs 1.4).

"This first head-to-head prospective study in axSpA showed that radiographic progression of the spine over 2 years was low, with no significant difference between secukinumab and adalimumab biosimilar and no additional safety aspects besides the ones that we know well," Prof. Baraliakos summarised. These interesting findings must be interpreted in the context of the inability to recognise rapid progressor patients, which are hard to define, and where such a comparative analysis cannot be performed.

1. Baraliakos X. Effect of secukinumab versus adalimumab biosimilar on radiographic progression in patients with radiographic axial spondyloarthritis: a randomized phase IIIB study. OP0059, EULAR 2023, 31 May–3 June, Milan, Italy.

Vascular inflammation may be characteristic of PsA

The comparison of the aortas of patients with psoriatic arthritis (PsA) with those of healthy controls revealed increased vascular inflammation in PsA. PET/CT scan results showed significant differences in the target-to-background ratio (TBR), even when adjusted for cardiovascular risk factors.

"As we know, patients with PsA are at increased risk of developing cardiovascular disease, and these PsA patients also have increased traditional risk factors, such as diabetes, obesity, or smoking. But this does not fully explain the

elevated cardiovascular risk in the PsA population," Dr Nienke Kleinrensink (UMC Utrecht, the Netherlands) explained the motivation for their research [1]. The retrospective Dutch study investigated whether inflammation in patients with PsA may also be present within the vascular system. As means of vascular inflammation determination, 18F-FDG PET/CTs with TBR of the aorta were used, a method that has been determined to be a reliable and reproducible measure [2,3].

The analysis included 75 PsA patients with active peripheral arthritis from an ongoing clinical trial (EudraCT 2017-003900-28) with a median age of 53, a median swollen joint count of 3, and a mean affected body surface area of 1 [1]. This cohort was compared with a control group of 40 melanoma patients without distant metastases, who neither had auto-immune disease nor were treated with checkpoint inhibitors. "We found no difference in age, blood pressure, or gender, but patients with PsA had a slightly higher BMI than the control group," Dr Kleinrensink commented on the baseline characteristics. Both groups comprised about 57% of men, and around 15% had prior cardiovascular disease.

The results showed significantly increased vascular inflammation in PsA versus controls, not only when evaluating the entire aorta (P≤0.001) but also in its 5 different sub-segments. These findings remained significant after a multivariate analysis that corrected for traditional cardiovascular risk factors, including age, sex, BMI, and mean arterial pressure.

"We also measured clinical measures of disease activity, such as tender joints count, swollen joints count, enthesitis index, BSA affected psoriasis, and inflammation parameters, but these were not associated with vascular inflammation assessed on PET/CT," Dr Kleinrensink informed.

In her summary, she said that the study confirms that there is indeed systemic inflammation going on in PsA. "It would be interesting for future studies to assess the effect of PsA treatment on vascular inflammation," Dr Kleinrensik concluded.

1. Kleinrensink NJ, et al. Increased vascular inflammation on PET-CT in psoriatic arthritis patients in comparison with healthy controls. OP0026, EULAR 2023, 31 May–3 June, Milan, Italy.
2. Rudd JHF, et al. J Am Coll Cardiol. 2007;50:892-6.
3. Bucerius J, et al. Eur J Nucl Med Mol Imaging. 2016;43:780-92.

Obesity in PsA is increasingly affecting male patients

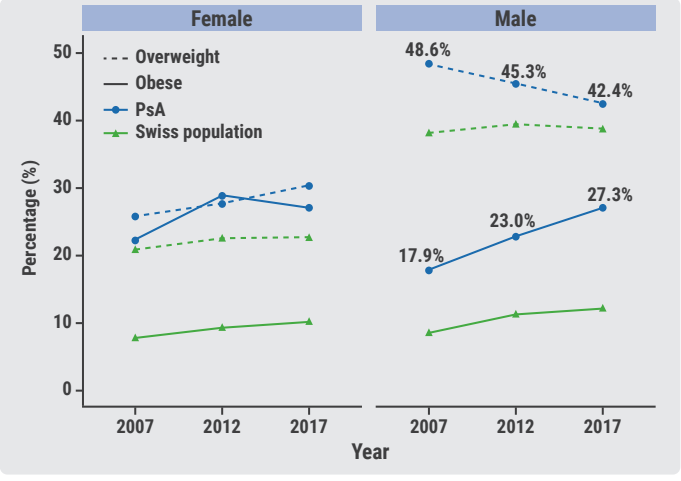
In a Swiss study, a substantially higher prevalence of obesity and overweight among patients with psoriatic arthritis (PsA) versus the general population was seen. Obesity increased in male PsA patients over time across all educational levels.

Dr Marlene Stirnimann-Agustoni (University Hospital of Zürich, Switzerland) and her group undertook a study to compare the prevalence of obesity and overweight in patients with PsA compared with that of the general population [1]. Additionally, they intended to examine the socioeconomic characteristics linked to overweight and obesity.

The researchers compared information on PsA patients (obtained from the Swiss Clinical Quality Management database) with data from the general Swiss population (obtained from the Federal Statistical Office). Individuals were divided into 4 groups based on their BMI: underweight (BMI <18.5), normal weight (BMI between 18.5 and <25), overweight (BMI between 25 and <30), and obese (BMI ≥30).

The PsA population size was 517 in 2007 and increased to 1,245 in 2017. During this time, the average BMI of patients with PsA increased from 26.6 in 2007 to 27.5 in 2017. The percentage of patients who were considered obese rose from 19.9% in 2007 to 27.2% in 2017. In male PsA patients, there was an even steeper increase (see Figure). Therefore, obesity is becoming increasingly common, particularly among male patients.

Figure: Prevalence of obesity and overweight according to sex in the Swiss population: in male PsA patients, there is a striking increase in obesity from 2007 to 2017 [1]



The study also showed that, regardless of sex, the prevalence of obesity and overweight was considerably greater in PsA patients than in the general Swiss population. While in the general population, higher educational levels were linked to

decreased proportions of obesity and overweight, patients with PsA showed identical proportions of obesity and overweight regardless of educational level. Unexpectedly, the difference between blue-collar and white-collar workers did not significantly affect the prevalence of obesity and overweight in PsA patients.

These results highlight the need for focused interventions to reduce obesity and its hazards in patients with PsA, regardless of educational background or occupation.

1. Stirnimann-Agustoni M, et al. Obesity in psoriatic arthritis is increasingly affecting men and appears less dependent of socioeconomic status than in the general population. OP0064, EULAR 2023, 31 May–3 June, Milan, Italy.

PsA patients: highest risk of developing NAFLD

Compared with patients with psoriasis (PsO) and other inflammatory arthritis (OIA), patients with psoriatic arthritis (PsA) have the highest risk of developing non-alcoholic fatty liver disease (NAFLD) and related liver fibrosis. Moreover, in PsA patients, fibrosis-4 (FIB-4) index scores showed a significant association with fibrosis, whereas ELF scores were not indicative of fibrosis.

Psoriatic disease (PsD), encompassing PsO and PsA, increases the susceptibility to developing NAFLD compared with other forms of inflammatory arthritis [1]. This risk persists despite disease-modifying antirheumatic drug (DMARDs) use and may rapidly progress to severe fibrosis [2].

Until present, a NAFLD screening pathway previously developed by the Leeds Teaching Hospitals NHS Trust (LTHT) is not validated in patients with PsD, highlighting the need for further research. Therefore, psychologist Anthony Harrison (Leeds Teaching Hospitals NHS Trust, UK) and his team conducted an audit to assess the prevalence of NAFLD in the PsD population [3]. Additionally, the team evaluated the effectiveness of the LTHT NAFLD pathway in accurately identifying PsD patients at risk of acquiring fibrosis or cirrhosis.

The study investigated consecutive patients presented at the Leeds Specialist Spondyloarthritis and Dermatology departments who underwent NAFLD screening using the LTHT pathway. The researchers categorised these patients into 3 groups according to the disease: PsA (n=60), PsO (n=38), and OIA (n=18).

Most demographic and clinical variables were similar across all 3 groups. However, the majority of the patients with OIA (66.6%) were males, and half were receiving biological DMARD monotherapy. In contrast, a large proportion of patients with PsO (60.5%) were not taking any DMARDs, and only 1 was under biological DMARD.

"We further screened these patients using ELF test scores combined with FIB-4 index scores. We selected those with ELF >9.5 or FIB-4 >1.45 and sought fibroscan and hepatology opinion," Mr Harrison explained. A fibroscan reading above 10 was considered indicative of clinically expressive NAFLD.

The findings revealed that patients with PsO had higher ELF scores, while patients with PsA displayed higher FIB-4 scores than all other groups. In the PsA group, higher FIB-4 scores showed a significant association with fibroscan scores above 10 (P=0.05) but not the ELF scores. An association between higher FIB-4 scores and diagnosis of liver fibrosis (P=0.09) was suggested.

Mr Harrison concluded that patients with PsA have higher rates of NAFLD fibrosis/cirrhosis than patients with PsO or OIA. Moreover, FIB-4 showed higher potential than ELF in identifying PsA patients at high risk of NAFLD fibrosis. A comprehensive prospective cohort study in the future is needed to validate these findings.

1. Prussick RB, et al. J Clin Aesthet Dermatol. 2015;8:43-45.
2. Prussick RB, et al. Br J Dermatol. 2017;179:16-29.
3. Harrison S, et al. Non-alcoholic fatty liver disease (NAFLD) in psoriatic disease (PsD): identifying patients at high risk of serious liver disease. POS0022, EULAR 2023, 31 May–3 June, Milan, Italy.

What is Hot in Osteoarthritis

Lorecivivint shows long-term benefits for severe knee OA

Lorecivivint showed potential benefit in radiographic and pain outcomes in an ongoing phase 3 extension trial in subjects with severe knee osteoarthritis (OA). Multiple injections appear to be a safe and effective treatment option.

Lorecivivint is a novel, intra-articular dual-specific tyrosine phosphorylation-regulated kinase (DYRKs)/CDC-like kinase (CLK) inhibitor. It is thought to modulate Wnt inflammatory and structural pathways at the nuclear level. Prof. Timothy McAlindon (Tufts University School of Medicine, MA, USA) emphasised that although there was not much change in medial joint space width (JSW) in the parent study, the STRIDES-X-ray trial, the extension was planned as there were significant findings concerning pain.

In this ongoing, single-blind, phase 3, long-term extension study (NCT04520607), 277 participants (about 50% of those who completed the parent trial) with structurally advanced knee OA (JSW of 1.5–4 mm) were enrolled [1]. At the beginning of the extension study, participants received a repeat injection according to the initial randomised treatment of either lorecivivint or placebo. At month 24 and annually thereafter, participants received an injection of 0.07 mg of lorecivivint.

The primary outcome measures consisted of medial JSW and pain Numerical Rating Scale (NRS). A potential benefit of lorecivivint compared with placebo in medial JSW was observed by month 24, with additional benefit following the third injection evident at month 36. At this time, a significant difference between active treatment and placebo at 24 months was noted, supporting the potential treatment effects of lorecivivint. Similarly, improvements in pain NRS were seen at month 36.

After 24 months, lorecivivint-treated participants also showed significant improvements in Western Ontario McMaster University Osteoarthritis Index (WOMAC) pain, assessed as a secondary endpoint. However, there was no difference at 36 months.

The compound remained safe and well tolerated, consistent with its previously observed safety profile.

1. Yazici Y, et al. Radiographic and pain outcomes from a phase 3 extension study evaluating the safety and efficacy of lorecivivint in subjects with severe osteoarthritis of the knee (OA-07): Single blind and crossover results. OP0074, EULAR 2023, 31 May–3 June, Milan, Italy.

Methotrexate lowers pain in inflammatory hand OA

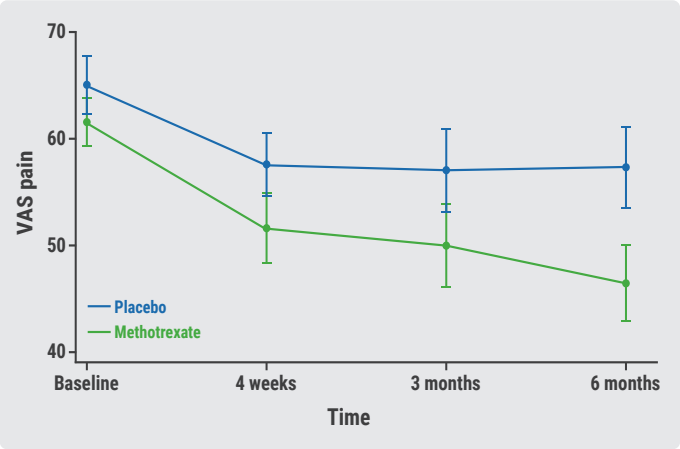
In a placebo-controlled study, therapy with methotrexate led to a clinically significant reduction of pain and stiffness in participants with osteoarthritis (OA) of the inflammatory phenotype. Methotrexate could become a novel, economical treatment possibility for these difficult-to-treat patients.

At present, limited therapeutic options are available for hand OA. A previous randomised-controlled trial showed no superiority of methotrexate 10 mg over placebo in pain relief at 3 or 12 months in participants with erosive hand OA [1]. However, as Prof. Flavia Cicuttini (Monash University, Australia) pointed out, hand OA is a heterogeneous disease, and no previous study has examined methotrexate in hand OA targeting the inflammatory subtype. "Our aim was to determine whether methotrexate reduced pain and improved function over 6 months in participants with hand OA and synovitis," she explained [2].

This multicentre, double-blind, randomised-controlled trial included participants with radiological OA in ≥1 joint and non-gadolinium MRI-detected synovitis, who were treated with methotrexate 20 mg/week or placebo plus folic acid 5 mg on other days. The primary outcome was pain reduction (assessed by a 100 mm visual analogue scale [VAS]) at 6 months.

Baseline characteristics were typical for an OA population with a medium age of 60 and a female preponderance. Regarding the primary study endpoint, there was an improvement in pain in both groups until week 4, but methotrexate kept reducing this symptom, whereas there was a plateau in the VAS in the placebo group (see Figure). At 6 months, the methotrexate group had a greater reduction in VAS pain than the placebo group (-15.2 vs -7.7; difference -9.9; 95% CI -19.3 to 0.6). "When we calculated the effect size, VAS pain was 0.45, which puts it into a moderate effect," Prof. Cicuttini explained. In addition, therapy with methotrexate also led to a distinct improvement in stiffness. Methotrexate was safe and well tolerated. The

Figure: VAS pain at each time point over the study period [2]



VAS, visual analogue scale.

study's limitations were that it was initially planned to assess methotrexate's effect on pain and radiographic progression over 2 years. However, all medication ceased in March 2020 due to uncertainty regarding the safety of methotrexate during the COVID-19 pandemic.

All in all, this study is proof of concept that methotrexate may have a role in the management of hand OA with the inflammatory phenotype. "Studies of longer duration including assessment of structural modification are warranted to see whether methotrexate has a disease-modifying effect as well," Prof. Cicuttini concluded.

1. Ferrero St, et al. Semin Arthritis Rheum. 2021;51:831-8.
2. Cicuttini F, et al. METHODS - A randomized controlled trial of METhotrexate to treat Hand Osteoarthritis with Synovitis. OP0070, EULAR 2023, 31 May–3 June, Milan, Italy.

Systemic Sclerosis: State of the Art

Targeted DMARDs advantageous in SSc patients with pre-capillary pulmonary hypertension

A significant benefit of targeted disease-modifying antirheumatic drugs (DMARDs) in patients with systemic sclerosis (SSc) and pre-capillary pulmonary hypertension (precapPH) was found in terms of a protective effect on mortality and worsening of precapPH. This outcome was independent of the presence of interstitial lung disease (ILD).

"We all know that precapPH is a life-threatening complication in SSc," Dr Cosimo Bruni (University Hospital Zurich, Switzerland) stated, further pointing out that its treatment currently relies on medications for pulmonary arterial hypertension or ILD [1]. As specific knowledge on the efficacy of targeted DMARDs on precapPH is still unsatisfactory, a retrospective observational study was performed to gain further insight into their possible benefit.

Patients with SSc from the EUSTAR registry with data on their immunosuppressive therapy and who fulfilled the haemodynamic criteria for precapPH after performing a right heart catheterisation were included. Immunosuppressive drugs included conventional synthetic DMARDs or targeted therapies (abatacept, rituximab, tocilizumab, TNF inhibitors, JAK inhibitors). The analysis focused on death or a predefined worsening of precapPH as the outcome, comparing patients with or without immunosuppressants. It also took into account a wide variety of potentially confounding covariates regarding risk stratification, among them gender, age, lung function, cardiac insufficiency markers, renal history, and medication levels.

Out of 755 patients, 82% were women, the mean age was 63 years, 29% had diffuse cutaneous SSc, and SSc with precapPH was present for a mean of 11 years. Half were treated with immunosuppressants, and 94% in this group had ≥1 conventional synthetic DMARD.

After a follow-up of 2.9 years, 72% had either died or experienced an event of pulmonary worsening. "These events were numerically higher in the immunosuppressants-exposed group, both for the combined outcome or for the separate outcomes (death or precapPH worsening)," Dr Bruni described.

Primarily, the Cox-regression modelling failed to find significance in the effect of immunosuppressants overall (P=0.551). However, after stratification according to the type of treatment, targeted therapy demonstrated a significant effect (P=0.021) on protection against the combined

outcome of death or precapPH worsening. As the presence or absence of ILD might have influenced this result, a further categorisation was performed that again yielded significance for targeted therapies (P=0.026), confirming that the effect was independent of ILD. "The signals that we noted were mostly related to tocilizumab, having a statistically significant protective effect, and a trend was also noted for rituximab," Dr Bruni further specified.

"Now, randomised clinical trials exploring targeted therapies should be designed using long-term morbidity and mortality outcomes to validate our results further and possibly improve the care of our patients," Dr Bruni recommended in his conclusion.

1. Bruni C. Immunosuppression with targeted DMARDs reduces morbidity and mortality in pre-capillary pulmonary hypertension associated with systemic sclerosis: a EUSTAR analysis. OP0238, EULAR 2023, 31 May–3 June, Milan, Italy.

Osteoporosis: New Data

Drugs for osteoporosis: time to reach fracture risk reduction varies

Most patients on anti-osteoporotic therapy achieve a reduced fracture risk on long-term treatment, but the time this takes may differ for each drug. After 2 years, more teriparatide-treated patients reached the surrogate threshold effect (STE) than patients on denosumab or bisphosphonates.

Bone mineral density (BMD) STE is described as the minimally necessary treatment effect on BMD that is predictive of reduced fracture risk with 95% certainty [1]. Dr Giovanni Adami (University of Verona, Italy) explained that the necessary thresholds were recently validated and found different, depending on the type of fracture intended to be reduced in risk [1,2]. The STE estimates for any minimum fracture risk reduction for all, vertebral, hip, and nonvertebral fractures were determined at 1.83%, 1.42%, 3.18%, and 2.13% [2].

The current study used longitudinal information from the DeFRA database between 2012 and 2022 [1]. It identified 1,523 women at high risk of fracture starting therapy with bisphosphonates, 390 with denosumab, and 104 with teriparatide. The mean age of this cohort was 68.2, 10-year major osteoporotic fracture risk was 15.7%, and the median follow-up time was 826 days.

Regarding the rates of patients reaching STE after 2 years of treatment, the proportions varied according to the treatment (see Table), type of fracture, and amount of risk reduction. Regarding all fractures, any risk reduction was achieved by 24.2% (bisphosphonates), 48.5% (denosumab), and 62.9% (teriparatide) at this time point. The respective proportions were 24.4%, 49.1%, and 62.9% for vertebral fractures and 21.4%, 46.9%, and 61.4% for hip fractures, respectively. Kaplan-Meier curves that estimated the likelihood of attaining a T-score higher than -2.5 differed according to treatment. For example, a patient with a T-score of -3.0 at baseline demonstrated a 35% chance of reaching osteopenic levels after 2 years on bisphosphonates but a 54% or 60% chance on denosumab or teriparatide.

"In the long term, if you follow up the patients for over 6 years, you will find that approximately 100% of patients with denosumab and 80% of patients on bisphosphonates reach the STE," Dr Adami underlined in his conclusion.

Table: Percentage of patients reaching various STEs, stratified by treatment, at 2 years [1]

Fracture risk reduction	STE (%)	Bisphosphonates (%)	Denosumab (%)	Teriparatide (%)
	All fractures			
Any	1.8	24.2	48.5	62.9
>30%	5.1	18.6	39.9	64.5
	Vertebral fractures			
Any	1.4	24.2	49.1	62.9
>50%	4.6	19.1	41.3	60.5
	Hip fractures			
Any	3.2	21.4	46.9	61.4
>30%	5.8	17.7	38.0	59.8

STE, surrogate threshold effect.

1. Adami G. Proportion of patients reaching the bone mineral density (BMD) surrogate threshold effect (STE) with bisphosphonates, denosumab and teriparatide. OP0242, EULAR 2023, 31 May–3 June, Milan, Italy.
2. Eastell R, et al. J Bone Miner Res. 2022;37:29-35.

Romosozumab: the new option for glucocorticoid-induced osteoporosis with high fracture risk?

When comparing the increase in bone mineral density (BMD) after 1 year of romosozumab with BMD after 12 months of denosumab, the adjusted rates were significantly higher in the romosozumab arm. The tolerance of both drugs was overall good.

Romosozumab is a humanised monoclonal antibody against sclerostin, with demonstrated efficacy in postmenopausal women with osteoporosis. However, until now, no data regarding its efficacy in glucocorticoid-induced osteoporosis has been available.

The 24-month, open, controlled trial (NCT04091243) included 70 adult patients receiving at least 5 mg of daily prednisolone for ≥1 year, who were randomised to either romosozumab (210 mg monthly) or denosumab (60 mg every 6 months) for 12 months, followed by 1 year of denosumab for both groups [1]. All participants had a moderate or high risk of osteoporotic fractures. The primary outcome was defined as the change in BMD of the lumbar spine at 12 months. The study protocol included suspending previous bisphosphonates therapy while continuing calcium and vitamin D treatment.

The study population had a mean age of 62.9 years, and 96% were women. The most frequent primary diagnoses were systemic lupus erythematosus (51%) and rheumatoid arthritis (29%). About half of the study cohort had a history of fragility fractures. "The mean prednisolone dose at entry was 6.6 mg/day, and bisphosphonates were used in around half of the patients at the time of recruitment," Dr Chi Chiu Mok (Tuen Muk Hospital, China) elaborated. At baseline, significant differences between the 2 study groups were not found.

The main results revealed significant increases of BMD in the lumbar spine at month 12: +7.3% in the romosozumab group (P<0.001) and +2.3% in the denosumab group (P<0.001), compared with baseline. Adjusting the results for baseline BMD, age, sex, and other osteoporosis risk factors, a significant difference between the treatment arms was found (P<0.001). The changes from baseline in hip and femoral neck BMD were also significant at 12 months; however, no inter-group difference was found. Concerning markers of bone turnover, both N-terminal propeptide of type 1 procollagen (P1NP) and carboxy-terminal collagen crosslinks (CTX) significantly dropped in the denosumab arm (P<0.001 and P=0.002), whereas a decrease in CTX and a slight rise in P1NP on romosozumab group were not significant (P=0.18 and P=0.89).

The most frequent adverse event was injection-site pain, which was present in 8 cases in the romosozumab group, but not in the denosumab arm. Dr Mok hypothesised that this difference was caused by the higher frequency of the romosozumab injections as they were given monthly, while denosumab injections occurred only twice in 1 year.

"Romosozumab may thus offer a new treatment option for glucocorticoid-induced osteoporosis in high-risk patients," Dr Mok concluded.

1. Mok CC. Romosozumab versus denosumab in high-risk patients with glucocorticoid-induced osteoporosis: a pilot randomised controlled trial. OP0246, EULAR 2023, 31 May–3 June, Milan, Italy

Best of the Posters

Therapy with biological DMARDs shows no correlation with fracture risk in RA

Patients with rheumatoid arthritis (RA) carry an almost 50% higher risk of major osteoporotic fractures (MOF) than patients without RA, according to the Norwegian HUNT study. The highest risk was noted in RA patients that had never used disease-modifying antirheumatic drugs (DMARDs).

Previous studies have shown that the incidence of osteoporosis among patients with RA is 1.9 times higher than among non-RA patients [1]. Although bone-sparing properties for biological (b)DMARDs have been demonstrated, the effect of different types of DMARDs on reducing fracture risk is yet to be explored in detail [2,3].

To answer this question, Ms Ingebjorg Tronstad (Norwegian University of Science and Technology, Norway) performed the

Trondelag Health Study (HUNT), a population-based longitudinal study including 96,354 participants who were classified based on whether or not they had RA according to existing patient records or per International Classification of Disease codes (ICD9 and 10) and the ACR/EULAR criteria [4]. Disease status was registered at baseline and updated if RA was diagnosed later. Accordingly, 1,033 patients had RA (mean age 46.3 years, 53% women), and 95,321 did not. Of the former, 401 were diagnosed before inclusion in the study and 632 during follow-up.

Any MOF diagnosed were also recorded, as well as the use of DMARDs. Ms Tronstad and her team classified patients into 3 groups: 57 patients who had never used DMARDs (never DMARDs), 727 patients using conventional synthetic (cs)DMARDs only, and 230 patients who had ever used bDMARDs. Participants were followed up until the first MOF, death, emigration, or end of follow-up in October 2021.

The results revealed that patients with RA, regardless of treatment, had an almost 50% increased risk of MOF compared with patients without RA (HR 1.44; 95% CI 1.25–1.65). Additionally, the incidence rates of MOF per 1,000 person-years were higher in RA overall and in all DMARD treatment groups compared with non-RA. After Cox regression analyses adjusted for age, sex, and smoking status, it was found that across the 3 treatment groups, never DMARDs had the highest risk of MOF (HR 2.05; 95% CI 1.28–3.31) followed by the csDMARDs group (HR 1.5; 95% CI 1.29–1.75). In contrast, treatment with bDMARDs did not significantly correlate with MOF (HR 1.03, 95% CI 0.70–1.50).

The authors concluded that, even though RA is associated with MOF, it is encouraging that individuals treated with bDMARDS had no association with MOF, which should be considered in future treatment regimens for RA patients.

1. Lee SG, et al. Int J Rheum Dis. 2012;15:289-96.
2. Chen JF, et al. Rheumatology (Oxford). 2020;59:2471-2480.
3. Shao F, et al. Eur Rev Med Pharmacol Sci. 2021;25:3416-3424.
4. Tronstad I, et al. Do disease modifying antirheumatic drugs influence the fracture risk in rheumatoid arthritis? The HUNT study. POS0175, EULAR 2023, 31 May–3 June, Milan, Italy

Bimekizumab: high rates of sustained response in PsA

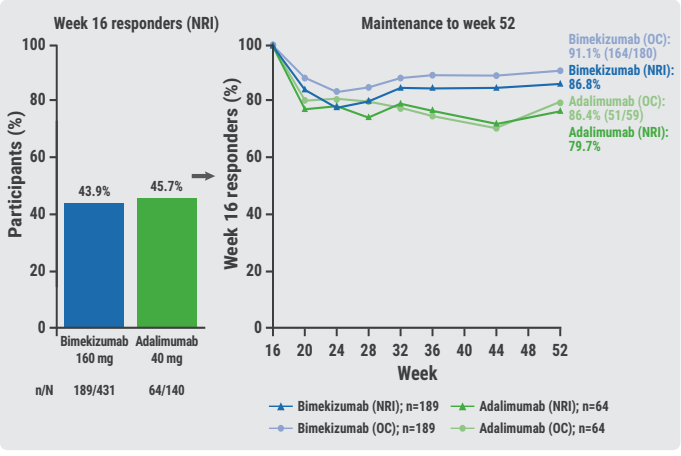
Participants with psoriatic arthritis (PsA) who had responded to bimekizumab at week 16 exhibited sustained effectiveness with this treatment for up to 52 weeks. Minimal disease activity was sustained by 85.6% and the ACR50 by 86.8% of these prior responders.

Long-term disease control is crucial in chronic disorders like PsA, especially as loss of response during treatment may be possible [1]. After demonstrating superiority over placebo at week 16 in the phase 3 BE OPTIMAL trial (NCT03895203), bimekizumab was investigated for its ability to maintain efficacy in participants with PsA [2]. The initial phase 3 cohort was randomised to bimekizumab, placebo, or adalimumab as active reference. A direct statistical comparison of the placebo arm and bimekizumab versus adalimumab could not be performed due to underpowering of the adalimumab group. The current analysis showed outcomes for responders at week 16, who were followed through a subsequent 36-week active treatment-blind period. The results were presented using non-responder imputation (NRI) as well as observed case (OC) reporting.

The baseline characteristics of the 431 participants treated with bimekizumab included a mean age of 48.5, a mean duration of PsA of 6 years, and a BMI of 29.2 kg/m^2. Also, enthesitis was present in about one-third, and the mean Psoriasis Area and Severity Index (PASI) score was 8.2.

The results after 1 year revealed that out of the initial 43.9% of participants on bimekizumab who achieved an ACR50 at week 16, 86.8% (NRI) and 91.1% (OC) were able to sustain their response at week 52. In the adalimumab reference arm, with 64 responders out of 140, the corresponding rates were 79.7% and 86.4% (see Figure). PASI100 was sustained in 79.6% on bimekizumab and 71.4% on adalimumab (both NRI). Minimal disease activity, reached by 45% in both active groups at week 16, persisted in 85.6% (bimekizumab) and 82.5% (adalimumab). Of note, the simultaneous maintenance of ACR50 and PASI100 was present at week 52 in 86.7% (NRI)

Figure: Maintenance of ACR50 responses at week 52, in week 16 responders [1]



NRI, non-responder imputation; OC, observed case.

or 89.7% (OC) participants receiving bimekizumab, and 54.5% (NRI) or 66.7% (OC) participants on adalimumab, respectively.

Up to year 1, a 79.1% rate of at least 1 treatment-emergent adverse event was observed in bimekizumab recipients, and 6.6% were reported as serious, which was in line with prior findings.
As comprehensive long-term disease control is important in PsA, the authors underlined that maintained robust efficacy responses were seen at week 52 in a high proportion of bimekizumab-treated initial responders from the BE OPTIMAL trial. Nearly 90% of participants persisted with a high level of response in both articular and cutaneous domains under bimekizumab, keeping in line with the previously recognised superiority of IL-17 pathway inhibition in the psoriasis space.

1. Boehncke WH, Menter A. Am J Clin Dermatol. 2013;14:377-88.
2. Tillett W, et al. Bimekizumab maintained efficacy responses through 52 weeks in biologic disease-modifying antirheumatic drug-naïve patients with psoriatic arthritis who were responders at week 16: results from BE OPTIMAL, a phase 3, active-reference study. POS1534, EULAR 2023, 31 May–3 June, Milan, Italy.

Basic Science

In vitro and *in vivo* studies confirm the role of regulatory volume decrease

Experimental *in vitro* and *in vivo* studies confirmed the important role of the so-called regulatory volume decrease (RVD), an endogenous defence mechanism that allows cells to return to their initial volume after cellular swelling. Moreover, LRRC8A seems to be the key protein required for this mechanism.

Acute arthritis induced by monosodium urate (MSU) and calcium pyrophosphate (CPP) crystals depends on IL-1β activated by the NLRP3 inflammasome. Different stimuli, such as hypo-osmolarity and ATP, can trigger the NLRP3 inflammasome. Secondary to water influx, there is cellular swelling. As an endogenous defence mechanism, cells set up the RVD, allowing cells to return to their initial volume. LRRC8A is the obligatory key protein required to form active VRAC channels, responsible for water efflux and cell volume reduction.

In their study, Dr Twinu Wilson Chirayath (Paris Cité University, France) and his team tried to evaluate the role of the LRRC8/VRAC channel in cell volume regulation and MSU- and CPP-crystals-induced release of IL-1β by stimulating primed monocytes with synthetic sterile MSU and CPP [1]. Cytokine production was then quantified by ELISA, and cell volume variations were visualised by live video recording. Moreover, the role of the LRRC8/VRAC channel was evaluated with the help of the pharmacological inhibitor DCPIB or by silencing the LRRC8A subunit (shLRRC8A RNA) in these cells.

In addition, the researchers injected MSU and CPP crystals into air pouches created subcutaneously (mimicking synovial cavity) in wildtype mice and conditional LRRC8A knock-out mice. Supernatants and pouch lavages were used to measure cytokine production by ELISA.

Both in cells treated with the pharmacological inhibitor and in cells where LRRC8A expression was silenced, MSU- and CPP-induced NF-Kb activation was markedly reduced. This was accompanied by a significantly reduced IL-1β production compared with wildtype cells ($P<0.001$). MSU and CPP crystals exposure induced a biphasic cell volume change characterised by a significant increase followed by a decrease induced by a RVD-like phenomenon. Cells treated with the pharmacological inhibitor or cells with silenced LRRC8A subunits did not show the biphasic cell volume changes, supporting that LRRC8A is required to form active VRAC channels.

The *in vivo* results confirmed the effects seen in the *in vitro* experiment: Inflammation induced by MSU and CPP crystals assessed in lavage fluid and by conventional histology was lower in LRRC8A knock-out mice as compared with wildtype mice both in terms of IL-1β production and cell infiltrate.

The authors concluded that MSU- and CPP-crystal-induced inflammation are involved in IL-1β release, and cell volume variation can be regulated by the LRRC8/VRAC channel. These findings add further complexity to crystal-induced inflammation and inflammasome activation.

1. Chirayath TW, et al. Monosodium urate and calcium pyrophosphate crystal-induced inflammation relies on cell volume regulation and LRRRC8/VRAC channel activation. OP0095, EULAR 2023, 31 May–3 June, Milan, Italy.