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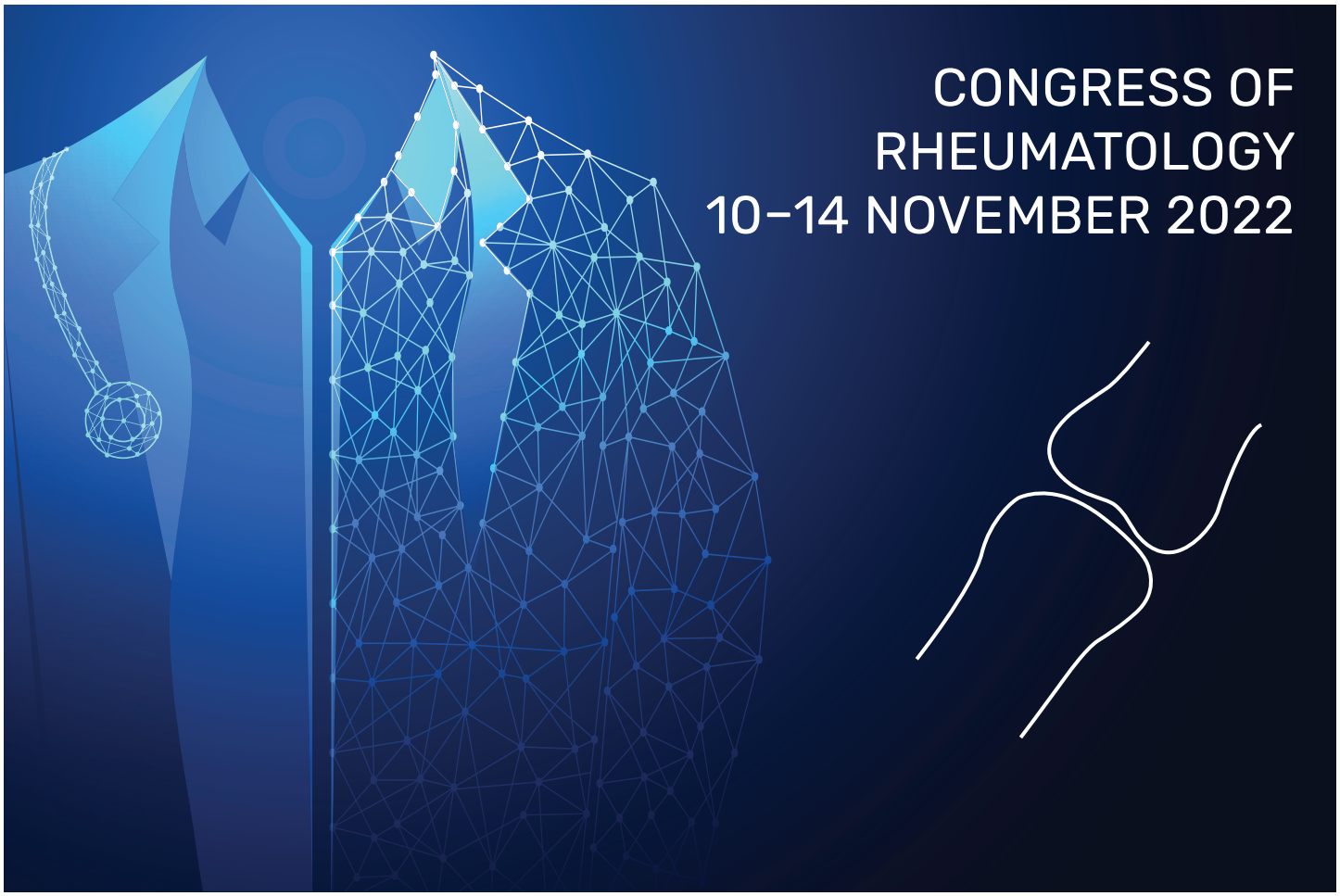


## Content

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# 1. Glucocorticoids in rheumatic diseases: Is there a skeletal sparing dose?

**Results of a cohort study that investigated changes in bone mineral density (BMD) on different regimens of glucocorticoids (GC) showed that even relatively low doses lead to significant bone loss in patients with inflammatory rheumatic musculoskeletal diseases (iRMD). Moreover, doses of 5 mg/day or higher doubled the fracture risk.**

Prompted by a recent trial (NCT02585258) that found a 4% difference in BMD between placebo and prednisolone-treated elderly patients with rheumatoid arthritis, a new Italian study strove to find out more about dose-dependency and anti-osteoporotic treatment [1,2]. The longitudinal cohort study included 884 women with iRMD who were propensity score-matched to 1,766 healthy women by age, T-score, and 10-year fracture risk [1].

The cohort's mean age ranged from 65 to 68, and over 85% were smokers. The median follow-up time was 2 years. The most frequent iRMD was rheumatoid arthritis (53.8%), and the mean T-scores of the femoral neck were -2.2 to -2.3. About 80% did not receive anti-osteoporotic therapy at baseline. In this subgroup of women, treatment with GC (noted in prednisone equivalent doses) entailed a significant seemingly dose-dependent BMD loss: -4.26% in those under prednisone ≥5 mg/day (P=0.0011), -4.23% in 2.5-5 mg/day (P=0.0422), and -2.66% in 0-2.5 mg/day (P=0.0006). Thus, interestingly, this reduction was not only present in patients with highly dosed GC. Dr Giovanni Adami (University of Verona, Italy), who presented the data, further stated that the women in the control group lost about 1.5% of BMD, which was to be expected in postmenopausal women. When patients on GC were treated with anti-osteoporotic medication, BMD was effectively increased only in the 2 groups on lower dosages of GC: from -4% to +3% (2.5-5 mg/day) and from -2.5% to +1% (0-2.5 mg/day). However, in the group with ≥5 mg/day, the loss was only reduced by 1% from -4% to -3%.

Additionally, patients with iRMD and without anti-osteoporotic treatment had a higher fracture risk than the matched controls. In the latter, an incidence of 2.2 fractures/100 person-years (PY) was reported. For patients on 1 of the 2 lower dose regimens of GC, the risk was about 30% higher, with 2.5 fractures/100 PY and 2.8 fractures/100 PY. The risk of those on high-dose GC (≥5 mg/day) was about twice as high (4.8 fractures/100 PY) compared with the controls.

All in all, Dr Adami suggested that the bone-safe dose could be less than 5 mg/day and that a dose ≥5 mg might entail a higher risk than expected. "Should we prevent or treat glucocorticoid-induced osteoporosis even if a very low dose of glucocorticoids is used?" he asked in his conclusions.


1. Adami G. Impact of glucocorticoid dosing and anti-osteoporotic treatment on bone health in patients with inflammatory rheumatic musculoskeletal diseases: a longitudinal cohort study. L01, ACR Convergence 2022, 10–14 November, Philadelphia, USA.
2. Boers M, et al. Ann Rheum Dis. 2022;81:925-36.


# 2. Bimekizumab: robust 1-year results in treating psoriatic arthritis

**The 52-week phase 3 results of the dual IL-17A/F inhibitor bimekizumab indicated sustained long-term efficacy. The safety profile was in line with previous investigations.**

The IL-17A and IL-17F inhibitor bimekizumab was evaluated for long-term safety and efficacy in the treatment of active psoriatic arthritis up to week 52 after demonstrating positive results at week 16 in phase 3 BE OPTIMAL trial (NCT03895203). The study included 852 patients, randomised 2:3:1 to placebo, bimekizumab 160 mg every 4 weeks, or adalimumab 40 mg every 2 weeks as the active reference group [1]. After week 16, an open-label phase started, and participants of the placebo and the bimekizumab group were treated with the study drug, while in the reference arm, medication with adalimumab remained unchanged.

The baseline features of the study cohort included a mean age of 48.7 years and 46.8% of men. Prof. Christopher Ritchlin (University of Rochester Medical Center, NY, USA) further highlighted that 58% of participants were on concomitant use of methotrexate, around half had at least 3% of psoriasis-affected body surface area, between 24.9% and 33.2% had enthesitis, and 7.9% to 13% had dactylitis. "Over 89% of patients completed week 52, with a low number of discontinuations due to treatment-emergent adverse events (TEAE) or lack of efficacy," Prof. Ritchlin pointed out.

After 1 year, an ACR50 response was achieved by 54.5% of participants on continuous bimekizumab, 53% of those who received placebo in the first 16 weeks and then switched to bimekizumab, and 50% of participants in the reference arm. The results for Psoriasis Area and Severity Index (PASI)100 were 60.8%, 65%, and 48.5% for each arm, respectively. "We were somewhat surprised by the high PASI100 rates for adalimumab, but it is important to know that only 68 patients were in this arm, so that may have influenced this particular outcome," Prof. Ritchlin commented. He further underlined that ACR20, ACR50, and ACR70 responses numerically increased from week 16 to week 52. After 1 year, minimal disease activity was present in 55% of participants on continuous bimekizumab, 53.7% of those receiving placebo/bimekizumab, and 52.9% of those treated with adalimumab. The radiographic progression inhibition was overall sustained in around 90% of all groups.

Comparing long-term safety between bimekizumab with the reference arm from weeks 0 to 52, the occurrence of any

TEAE and serious TEAE was 79.1% versus 80.7% and 6.6% versus 7.1%, respectively. Nasopharyngitis, upper respiratory tract infections, and urinary tract infections were the most common TEAE on bimekizumab (12%, 7.1%, and 6.1%). "Oral candidiasis was observed in about 5% of the patients on bimekizumab, which is significantly higher than what we saw with adalimumab, not unexpectedly," Prof. Ritchlin added.

In his summary, he underlined that these results represent long-term efficacy and tolerability for bimekizumab in patients with psoriatic arthritis, naïve to prior biologic treatment.

1. Ritchlin CT. Bimekizumab treatment in biologic DMARD-naïve patients with active psoriatic arthritis: 52-week efficacy and safety results from a phase 3, randomised, placebo-controlled, active reference study. L02, ACR Convergence 2022, 10–14 November, Philadelphia, USA.

## 3. Stimulation of PD-1: a new concept to treat RA

**Peresolimab was significantly superior to placebo in reducing the Disease Activity Score-28 with C-reactive protein (DAS28-CRP) as well as Clinical Disease Activity Index (CDAI) in patients with rheumatoid arthritis (RA). The safety profile did not demonstrate a dose effect of the study drug.**

The programmed cell death protein 1 (PD-1) agonist peresolimab represents a novel mode of action for the therapy of RA. "We hypothesised that peresolimab binding to PD-1, which is a checkpoint inhibitory receptor, could stimulate physiological immune pathways and restore immune homeostasis," Prof. Paul Emery (University of Leeds, UK) informed [1].

The presented phase 2a trial (NCT04634253) enrolled participants with moderate-to-severe active RA who had a prior failure to not more than 2 conventional synthetic, biologic, or targeted synthetic DMARDs. In this study, 98 participants were randomly allocated to a high (700 mg) or low-dose (300 mg) arm of peresolimab every 4 weeks or placebo. The change in DAS28-CRP represented the primary endpoint assessed at week 12, ending the first period of the study. At week 14, a further evaluation identified participants who had reached low disease activity defined by CDAI ≤10. They entered period 2 and stayed on 1 of the dosages of the active drug until week 24. All others continued on the standard of care.

The trial population was predominantly female, had a mean age between 50.1 and 55.8 years, and their RA had been present for around 10 years. Among the participants, 36.7% to 48% were experienced in biological or targeted synthetic DMARDs, and about 60% were on corticosteroids.

At week 12, the primary endpoint was met with significantly lower DAS28-CRP in both peresolimab arms than in the placebo arm ($P<0.05$ for the lower and $P<0.001$ for the higher dose). "CDAI also produced significant improvements, showing superiority over placebo, so, at the joint level, this drug clearly works," Prof. Emery further stated. When stratified according to prior use of DMARDs, naïve participants did not have better results than those who were experienced. "There is certainly no loss of response in the advanced therapy experienced patients," Prof. Emery commented. He also pointed out that participants with low disease activity at week 14 largely maintained their level of change in DAS28-CRP to the end of period 2.

Overall, the safety profile of peresolimab was considered acceptable. "No adverse event was more frequent in the higher dose than in placebo or the lower dose," Prof. Emery stated. Of note, nausea was reported in 4 participants (8.2%) on the higher dose during period 1, but it did not persist after they continued medication in period 2.

In summary, Prof. Emery pointed out that this data represents the first clinical evidence that agonism of checkpoint inhibitory receptors could be an effective approach to treating rheumatic diseases. Thus, peresolimab should be further evaluated.

1. Emery P. A phase 2 trial of peresolimab for adults with rheumatoid arthritis. L03, ACR Convergence 2022, 10–14 November, Philadelphia, USA.

## 4. Denosumab in erosive hand arthritis: Structure repair of interphalangeal joints seems possible

**Denosumab significantly led to remodelling and reduced progression in erosive hand osteoarthritis (OA). The treatment with twice the dose typically used in osteoporosis did not raise safety concerns.**

Exploring new treatment options for erosive hand OA, a Belgian team of investigators conducted a phase 2 trial (NCT02771860) to test the receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor denosumab for its potential in this setting [1].

In this proof-of-concept study, 100 adult patients with radiographically proven erosive hand OA were randomised to denosumab 60 mg every 12 weeks or placebo. Eligible patients needed to have radiographic evidence of erosions or joint space loss as well as inflammatory signs of interphalangeal joints.

The primary endpoint consisted of the change in the Ghent University Scoring System (GUSS) at week 24. "Positive changes indicate remodelling or repair, while negative changes show erosive progression," Prof. Ruth Wittoek (Ghent University Hospital, Belgium) clarified. After 48 weeks in the placebo-controlled period, participants could decide to enter an open-label extension up to week 96.

The study population was predominantly female (around 80%), the mean age was 61 years, and the mean disease duration was 6 years. The average observed number of affected interphalangeal joints in both hands was just under 4. Regarding the primary endpoint, the mean change in GUSS was higher with denosumab compared with placebo (6.0 in the denosumab arm and -2.8 in the placebo arm; P=0.024). This shows that the treatment group exhibited signs of remodelling, while the erosion progressed in the placebo group. This difference grew until week 48: 10.1 (denosumab) versus -7.9 (placebo), resulting in a stronger level of evidence (P=0.003). "During the open-label extension, the denosumab-treated patients continued to increase to show remodelling, while the former placebo-treated group, now also receiving denosumab, showed new signs of remodelling, so no more erosive progression," Prof. Wittoek further elaborated. Among the secondary endpoints, the development of new erosive joints at week 48 also reflected the superiority of denosumab over placebo: 1.8% compared with 7.0% (P<0.001). The decrease in pain and functional impairment was not significant in the trial's first phase. However, differences between those who started on denosumab and those who switched from placebo at week 48 were present at week 96 (P=0.028 for pain reduction and P=0.025 for functional impairment).

The safety profile showed 125 adverse events in the placebo arm and 98 in the denosumab group. Serious adverse events occurred in 7 participants in both groups and led to discontinuation in 3 cases each. Overall, no new safety concerns came to light on the double-dosing regimen.

"This is the first proof-of-concept study that suggests that structure modification is an achievable goal in patients with erosive hand OA. RANKL is a promising target in treating erosive hand OA," Prof. Wittoek concluded.

1. Wittoek R. Effect of denosumab on structure modification in erosive hand osteoarthritis: results of a 48-week, monocentric, randomised, placebo-controlled, double-blind phase 2 study and open label extension phase. L05, ACR Convergence 2022, 10–14 November, Philadelphia, USA.

## 5. High retention rates after switching between infliximab biosimilars

**A Danish observational study revealed that retention rates after biosimilar-to-biosimilar infliximab switch is high among patients with rheumatic diseases in daily practice. Higher retention rates were observed in patients previously treated with the originator biologic.**

As Dr Hafsah Nabi (Rigshospitalet, Denmark) pointed out, biosimilars play an important role in rheumatology, especially due to their economic advantage [1]. Evidence for their use is mainly based on randomised controlled trials. "We are missing data across indications in older age and in patients with complex comorbidities," Dr Nabi said. In addition, data regarding the outcomes after switching from one infliximab biosimilar to a second one is limited.

Denmark is known for its biosimilar success. Since 2015, switches have been mandatory, at the beginning from the original product to a biosimilar, but later from 1 biosimilar to another. In her study, Dr Nabi assessed the effectiveness of switching infliximab biosimilars CT-P13 to GP1111 among patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA). Patients were analysed in 2 cohorts: those who had previously switched from the originator (originator-experienced) and those who were originator-naïve. Data from the DANBIO registry linked with national patient registries were used, the latter to identify comorbidities.

The main outcome measures in the 2 groups were 1-year GP1111 treatment retention and changes in disease activity 4 months before versus 4 months after the switch. The researchers also identified clinical factors at baseline associated with GP1111 treatment withdrawal.

Included were 1,605 patients (685 RA, 314 PsA, and 606 axSpA) with a median disease duration of 9 years, of which 1,171 were originator-naïve. The originator-naïve group tended to be younger, with lower disease duration, but higher disease activity.

One-year retention rates of GP1111 were 92% (95% CI 90-95%) in the originator-experienced and 83% (95% CI 81-85%) in the originator-naïve, respectively. Changes in disease activity 4 months pre- and post-switch were close to zero for all disease activity measures (e.g. Disease Activity Score in 28 joints [DAS28], Ankylosing Spondylitis Disease Activity Score [ASDAS], pain Visual Analogue Scale [VAS]).

Factors associated with higher GP1111 retention rates were being originator-experienced compared to originator-naïve in the fully adjusted cohort (HR=0.36; 95% CI 0.2-0.7) and lower disease activity at baseline.

"Overall, the 1-year retention rates after biosimilar-to biosimilar infliximab switch was high. Moreover, the disease activity remained stable 4 months before and after switch," Dr Nabi summarised. The fact that retention was higher in originator-experienced patients and in patients with low disease activity suggests that outcomes are predominantly affected by patient- rather than drug-related factors.

1. Nabi H. Biosimilar-to-Biosimilar Switching in Routine Care – Results on >1,600 Patients with Inflammatory Arthritis in the DANBIO Registry. 1112, ACR Convergence 2022, 10–14 November, Philadelphia, USA.

## 6. New analysis assesses the safety of tofacitinib regarding extended MACE

**A new post-hoc analysis of the ORAL Surveillance study revealed that the risk of a composite of all ischaemic cardiovascular (CV) events and heart failure with tofacitinib appears similar to that with TNF inhibitors. However, the totality of CV risk was elevated with the higher tofacitinib dose versus the TNF inhibitor, most likely due to a higher incidence of venous thromboembolic events (VTE) in patients with rheumatoid arthritis (RA) treated with the JAK inhibitor.**

The black box warning of the FDA for JAK inhibitors issued in January 2022 was prompted by the recently published ORAL Surveillance trial (NCT02092467), a post-authorisation safety study of tofacitinib in 2 doses versus TNF inhibitors [1]. This study found an increased risk of major adverse cardiovascular events (MACE) and VTE with tofacitinib versus TNF inhibitors in patients with RA and at least 1 additional CV risk factor [1]. In addition, a post-hoc analysis of this trial revealed a higher risk of MACE with tofacitinib versus TNF inhibitors in patients with a history of atherosclerotic CV disease (ASCVD) [2]. In both these analyses, MACE consisted of a 3-component endpoint (MACE-3): CV death, non-fatal myocardial infarction, and non-fatal stroke.

A new post-hoc analysis presented by Prof. Maya Buch (University of Manchester, United Kingdom) expanded the 3 MACE components by evaluating the risk of all adjudicated CV events with tofacitinib compared with TNF inhibitors [3]. Extended MACE endpoints were based on MACE-3 and sequentially added adjudicated ischaemic CV events, in particular: hospitalisation for unstable angina (in MACE-4), coronary revascularisation procedures (MACE-5), transient ischaemic attack (MACE-6), peripheral vascular disease (MACE-7), and hospitalisation for heart failure (MACE-8). For example, MACE-4 included the risk of MACE-3 plus unstable angina, MACE-5 represented the risk of MACE-4 plus coronary revascularisation procedures, and so on. The totality of CV risk was defined by MACE-8 plus VTE.

"Baseline characteristics were well balanced, with hypertension being the most frequent comorbidity," Prof. Buch explained. When the researchers analysed the risk of extended MACE endpoints, they noticed that the risk diminished from MACE-4 to -7 with tofacitinib versus TNF inhibitors. "In MACE-7, there was no significant difference compared with TNF inhibitors," Prof. Buch said. The risk of MACE-8 was similar between both tofacitinib doses and TNF inhibitors. However, the risk of MACE-8 plus VTE was only similar with tofacitinib 5 mg versus TNF inhibitors (HR 1.12; 95% CI 0.82-1.52) but higher with tofacitinib 10 mg versus TNF inhibitors (HR 1.38; 95% CI 1.02-1.85), driven by an increase in VTE.

Whereas the cumulative probability of MACE-3 differed significantly between tofacitinib and TNF inhibitors, the curves of MACE-8 were largely superimposed with only a slight difference in the high tofacitinib dose. However, across extended MACE endpoints, the risk was also numerically higher with tofacitinib versus TNF inhibitors with a history of ASCVD.

A limitation of the analysis was that only low numbers could be included in individual CV events.

"This data highlights the need for a better understanding of the risk of individual CV events in patients with RA," Prof. Buch concluded.


1. Ytterberg SR, et al. N Engl J Med. 2022;386:316-26.
2. Charles-Schoeman et al. Ann Rheum Dis. 2022:ard-2022-222259. Epub ahead of print.
3. Buch M, et al. Risk of extended major adverse cardiovascular event endpoints with tofacitinib vs TNF inhibitors in patients with rheumatoid arthritis: a post hoc analysis of a phase 3b/4 randomised safety study. L06, ACR Convergence 2022, 10–14 November, Philadelphia, USA.


## 7. Lack of vaccination results in a higher frequency of pre-term births in pregnant women with rheumatic disease and COVID-19

**A study involving women with rheumatic and musculoskeletal diseases (RMDs) and SARS-CoV-2 infection during pregnancy evaluated the obstetric outcomes according to COVID-19 vaccination status. Unvaccinated women experienced a numerically higher occurrence of pre-term births than those who had received more than 1 dose of a COVID-19 vaccine.**

A descriptive study explored the obstetric outcomes based on COVID-19 vaccination status in pregnant women with RMDs who developed COVID-19 during pregnancy [1]. All data was retrieved from the COVID-19 Global Rheumatology Alliance (C19 GRA) registry, which collects information on COVID-19 infections in patients with RMDs.

Dr Sinead Maguire (St. James' Hospital, Ireland) and her research team selected pregnant women in the C19 GRA registry from 24 March 2020 to 25 February 2022. Additional data was collected via e-surveys sent to healthcare professionals who previously submitted data on pregnant patients to the C19 GRA registry.

The study stratified obstetric outcomes by the number of COVID-19 vaccine doses received before SARS-CoV-2 infection in pregnancy. "We defined those who have received 0 or 1 dose of COVID-19 vaccine as unvaccinated and those who had at least 2 doses as fully vaccinated," Dr Maguire described.

There were 73 pregnancies in 73 women, with a mean age of 32.3 years. The most common RMD was systemic lupus erythematosus (23.3%, n=17), followed by rheumatoid arthritis (21.9%, n=16). RMD was in remission at the time of COVID-19 diagnosis

in 69.9% (n=51) of the study cohort, whereas only 4.1% (n=3) exhibited severe disease activity. Others had mild to moderate disease status.

During the data collection period, 24.7% (n=18) of pregnancies were ongoing, while of the 55 completed pregnancies, 90.9% (n=50) resulted in live births. There was 1 miscarriage, 3 stillbirths, and 1 medical abortion for maternal health.

In the study cohort, 64.4% were unvaccinated (60.3% [n=44] had no dose received, 4.1% [n=3] received 1 dose), and the others were fully vaccinated. Although 20.5% (n=15) required hospital admission, only 16.4% (n=12) demanded COVID-19-specific pharmacological treatment.

COVID-19 infection during pregnancy was followed by delivery in 6.8% (n=3) of unvaccinated women and 3.8% (n=1) of vaccinated women. Moreover, of the completed pregnancies, there was a higher number of pre-term births in unvaccinated women than in vaccinated women (29.5% vs 18.2%; P=0.45).

The most frequent neonatal complication among live births was the low birth weight (birth weight <2500 g) recorded in 24% (12/50) of pregnancies.

In summary, unvaccinated pregnant women with RMDs and COVID-19 showed a trend towards an increased number of pre-term births than those fully vaccinated. "Our research findings support the active promotion of COVID-19 vaccination in women with RMD who are pregnant or planning a pregnancy," Dr Maguire concluded.

1. Maguire S, et al. Obstetric Outcomes in Women with Rheumatic disease and COVID-19 in the Context of Vaccination Status: Data from the COVID-19 Global Rheumatology Alliance Registry. 0950, ACR Convergence 2022, 10–14 November, Philadelphia, USA.

## 8. Ankylosing spondylitis: Combining biologics with NSAID does not imply reduced radiographic progression

**When comparing treatment with golimumab alone with a combined therapy that adds celecoxib, the latter was unable to slow down the progression of radiographic axial spondyloarthritis (r-axSpA). Only patients with a high risk for progression might benefit from combination therapy.**

To date, it is still unclear whether or not a potential additional value of NSAID treatment exists for the prevention of radiographic spinal progression in r-axSpA [1]. Therefore, Dr Fabian Proft (Charité University Hospital, Germany) and his team conducted the phase 4 CONSUL study (NCT02758782) that investigated if combining anti-TNF with an NSAID, i.e. celecoxib could result in delayed onset of structural damage of the spine in r-axSpA.

Before entering the trial, all included patients had high disease activity with a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of at least 4. Furthermore, the participants showed risk factors for radiographic progression as indicated by increased C-reactive protein (CRP) or the presence of syndesmophytes. During a run-in over 12 weeks, 128 enrolled patients were treated with golimumab 50 mg every 4 weeks. Those who responded with a reduction of at least 2 points in BASDAI (n=109) at week 12 were randomised to 96 weeks of either continuing on monotherapy with the TNF inhibitor or a daily addition of celecoxib 400 mg. The primary endpoint consisted of the difference in change of modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) between groups at week 108.

Baseline features of the study cohort showed a mean age of 38.7, 74.3% men and a mean BASDAI of 6.1. More than half already had ≥1 syndesmophyte, 87.6% were HLA-B27 positive, and the mean mSASSS was 11.9. As for the primary outcome of change in mSASSS, the difference between groups failed to reach statistical significance: 1.1 versus 1.7 (P=0.79). The growth of new syndesmophytes numerically favoured the combination treatment but also lacked statistical significance (11.1% on combination therapy vs 25% on golimumab monotherapy; P=0.12).

Overall, 327 adverse events were noted with golimumab alone and 353 with the combination with celecoxib, most commonly in terms of infections. Serious adverse events during phase 2 of the study occurred in 12 participants, with 5 in the monotherapy group. Study discontinuation due to side effects was also higher in the combination arm (4:1).

"The observed numerical reduction in radiographic spinal progression associated with the combined treatment of celecoxib plus golimumab might be relevant in high-risk patients," Dr Proft remarked during his conclusions.

1. Proft F, et al. Comparison of the effect of treatment with NSAIDs added to anti-TNF therapy versus anti-TNF therapy alone on progression of structural damage in the spine over two years in patients with ankylosing spondylitis (CONSUL): an open-label, randomised controlled, multicentre trial. 0546, ACR Convergence 2022, 10–14 November, Philadelphia, USA.

# 9. Diet and exercise program: a successful OA strategy in a community-based setting

**In a community-based setting, an adaptation of diet and an exercise programme led to modest improvements in pain in obese patients with osteoarthritis (OA). Remarkably, patients were able to lose 8% of body weight and had significant improvements in a couple of secondary outcomes.**

Weight loss and exercise programmes have been shown to be effective in academic, centre-based trials under highly controlled conditions. "However, these interventions have not been rigorously tested in community-based settings," said Prof. Stephen Messier (Wake Forest University, NC, USA) [1]. Therefore, the primary aim of his study was to determine whether adaptation to a diet and an exercise programme resulted in a statistically significant reduction in pain, compared with a control group.

Thus, 823 patients with OA were randomised and allocated to a diet and exercise group (n=414) or a control group (n=409). The primary outcome was the between-group difference in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) knee pain at the 18-month follow-up. The exercise programme consisted of 15 minutes of walking and 20 minutes of weight training, followed by another 15 minutes of walking. Patients were advised to practice 3 times a week for 18 months. In addition, they received recipes to compose a reduced-calorie diet of their choice with the option to include a nutritional powder to make low-calorie shakes as meal replacements. The control group received nutrition and health education in 5 1-hour face-to-face meetings over the 18 months and informational packets or phone sessions.

The baseline characteristics of both groups were comparable, with a median age of 64 years, a female predominance, and a BMI of 36.7.
Patients in the intervention group achieved a significantly lower WOMAC pain score after 6 and 18 months. At the end of the follow-up period, the WOMAC pain score was reduced by 32% in the intervention group compared with 24% in the control group (P=0.02). Moreover, patients in the intervention group were 20% more likely to attain a 2-point improvement in the WOMAC pain score (considered clinically meaningful) than the control group.

A remarkable success of the diet and exercise programme was noted regarding weight loss: Patients in the intervention group lost 8 kg, which is an 8% weight loss compared with only 2 kg in the control group (P>0.01). The former group also improved WOMAC function: They had a 36% better function compared with 22% in the control group (P<0.001). The intervention also led to a significantly higher mean 6-minute walking distance and a better health-related quality of life.

Prof. Messier concluded that a community-based exercise programme and dietary advice led to a statistically significant albeit modest reduction in pain. In addition, the remarkable weight loss seen in the intervention group can have important additional health benefits.

1. Messier S, et al. Effectiveness of Intensive Diet and Exercise on Knee Pain Among Communities with Knee Osteoarthritis, Overweight, and Obesity: The WE-CAN Pragmatic Randomized Clinical Trial. 1675, ACR Convergence 2022, 10–14 November, Philadelphia, USA.

# 10. Bruton's tyrosine kinase inhibition: a novel treatment option for Sjögren's syndrome?

**In a phase 2 study, remibrutinib significantly reduced objective disease parameters in patients with Sjögren's syndrome (SS). The agent also lowered immunoglobulins and disease-related autoantibodies, and was relatively well tolerated.**

Today, SS is considered a B-cell-driven disease, resulting from abnormal responses to autoantigens causing chronic inflammation of the exocrine glands [1]. Clinical symptoms commonly include oral and ocular dryness, fatigue, and joint pain [1]. Bruton's tyrosine kinase (BTK) plays a crucial role in B-cell receptor signalling. Inhibition of BTK has therefore emerged as a potential therapeutic option for selective immune modulation in a wide spectrum of diseases and has already been shown to be efficacious in chronic urticaria [2].

The LOUiSSE study (NCT04035668) is a phase 2 clinical trial to evaluate the safety and efficacy of the novel BTK inhibitor remibrutinib in patients with moderate-to-severe SS [3].

Included were 72 patients with SS classified according to the 2016 ACR/EULAR SS criteria, who were treated with 2 doses of remibrutinib or placebo. "Only patients with a residual unstimulated salivary flow rate of >0 ml/min were included," said Prof. Thomas Dörner (Charité University Hospital, Germany). The primary efficacy endpoint was a change from baseline in the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) score at week 24. Changes in patient-reported outcomes, such as the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), were secondary endpoints. "Very importantly, the study also compared twice versus once-daily dosing," Prof. Dörner said.

Baseline demographics were similar between groups. "Owing to the similar results between twice and once-daily dosing, we combined the 2 dosing arms and compared them with placebo," Prof. Dörner explained. The study was positive for the primary endpoint: ESSDAI was significantly reduced by -2.86 (P=0.003) in the remibrutinib arm compared with the placebo arm.

No treatment effect was seen on the ESSPRI score compared with placebo, including the 3 ESSPRI subdomains (dryness, pain, and fatigue). However, remibrutinib showed a trend towards improved unstimulated salivary flow.

Remibrutinib decreased the cytokine CXCL13 levels early on, whereas, in the placebo group, levels of this biomarker remained elevated. In addition, the BTK inhibitor modulated IgG and IgM as signatures of disease activity, with the strongest effects on IgM levels. The reduction of these immunoglobulins correlated with the decrease of anti-SSB and anti-SSA antibodies in the remibrutinib arm from baseline to week 24.

The agent had a favourable safety profile and was well tolerated in patients with SS over 24 weeks. Prof. Dörner concluded that remibrutinib is a potentially effective oral disease-modifying therapy for SS, which will be established in longer-term studies. The lack of effect on patient-reported outcomes may result from the relatively short treatment duration (24 weeks).


1. Brito-Zeron P, et al. Nat Rev Dis Primers. 2016;2:16047.
2. Maurer M, et al. J Allergy Clin Immunol. 2022;S0091-6749(22)01181-2.
3. Dörner T. Remibrutinib (LOU064) in Sjögren's Syndrome: safety and efficacy results from a 24-week placebo-controlled proof-of-concept study. 1113, ACR Convergence 2022, 10–14 November, Philadelphia, USA.


## 11. A novel risk score helps identify interstitial lung disease in patients with systemic sclerosis

**Although patients with systemic sclerosis-related interstitial lung disease (SSc-ILD) present with characteristic changes in high-resolution computed tomography (HRCT), a considerable percentage do not undergo imaging, especially during follow-up visits. Therefore, researchers developed a score to enable physicians to identify at-risk patients.**

ILD is identified in most patients with SSc and is the leading cause of SSc-related mortality [1]. HRCT is the gold standard for diagnosis. However, some physicians do not regularly perform baseline HRCTs in all patients. "Our previous survey identified that only about 66% of physicians regularly screen for ILD with HRCT at the time of SSc diagnosis, and this percentage drastically drops to less than 15% during follow-up visits," explained Dr Cosimo Bruni (University of Zürich, Switzerland) [2]. Therefore, Dr Bruni and his research group aimed to develop a risk score for the presence of SSc-ILD (the ILD-RISC score) to guide physicians in ordering both baseline and follow-up HRCTs.

For the identification of SSc-ILD, 13 variables were considered important: sex, age, disease duration from first non-Raynaud's phenomenon sign or symptom, skin subset, presence of oesophageal symptoms, current or past digital ulcers, arthritis, smoking, increased inflammatory markers, New York Heart Association (NYHA) class, positive SSc-related autoantibodies, the percentage of forced vital capacity (FVC%), and the percentage of diffusing capacity for carbon monoxide (DLCO%).

The prediction model for ILD was developed from baseline visits of SSc patients in 6 European referral centres using multivariable logistic regression with backward selection. Of the 780 included patients, 533 (43% ILD) and 247 (48% ILD) were randomly assigned to the derivation and validation cohorts.

In the derivation cohort, a model including FVC%, DLCO%, digital ulcers, age, and SSc-related autoantibodies showed an OR of 133.9 (95% CI 53.4-335.9) for the presence of ILD on HRCT. An ILD-RISC score ≥0.3 showed comparable precision and accuracy in the derivation, validation, and longitudinal cohorts, with a sensitivity of 85.6% and specificity of 53.6%.

Among 819 patients with negative baseline HRCT, 170 (20.8%) developed ILD during a 3.8 ± 3.0 years follow-up. Longitudinally, in almost 50% of visits (n=914/1809), HRCT could be correctly skipped following an ILD-RISC score <0.3.

"We still recommend performing HRCT screening in all patients if the test is readily available and patients are willing to undergo it so as not to miss any patient with ILD. However, in situations where HRCT is unavailable, our ILD-RISC score supports the ability of HRCT to identify this complication. Most important, it may help to decide when to order HRCTs at follow-up, thus limiting unnecessary exams," Dr Bruni explained.

A limitation of the score is its relatively low specificity, leading to a certain number of false positives.
"We are already working to improve the score further and continue to reduce the number of unnecessary HRCTs," he concluded.


1. Fischer A, et al. Open Access Rheumatol. 2019;11:283-307.
2. Bruni M, et al. Developing a screening tool for the detection of interstitial lung disease in systemic sclerosis: the ILD-RISC risk score. 1526, ACR Convergence 2022, 10–14 November, Philadelphia, USA.

# 12. Early treatment: a key to improved outcomes in polyarticular JIA

**Patients with polyarticular Juvenile Idiopathic Arthritis (pJIA) are more likely to achieve clinical remission with a combination of conventional and biological disease-modifying anti-rheumatic drugs (DMARDs) compared with the far more common approach of step-up therapy. Moreover, patients in the early combination group spent more time in clinically inactive disease (CID).**

"We know that pJIA patients are at risk of poor outcomes, and we do not have much evidence to support the best time to start biologics," said Prof. Yukiko Kimura (Hackensack Meridian School of Medicine, NJ, USA) [1]. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) developed 3 consensus treatment plans that differ when biologics are started [2]. The goal of the ongoing prospective, observational study STOP-JIA (NCT02593006) was to identify the optimal timing for starting biologics in untreated pJIA using the CARRA treatment plans. At the ACR meeting, Prof. Kimura presented the 3-year outcomes.

The following 3 CARRA treatment arms were assessed [1]:

- Step-up: methotrexate monotherapy with a biologic added after 3 months if needed;
- Early Combination: conventional DMARD and biological DMARD started together;
- Biologic First: biologic monotherapy.

The study collected data from the CARRA Registry every 3 months for the first 12 months and every 6 months thereafter.
The study endpoints at 3 years were CID off glucocorticoids, the clinical Juvenile Arthritis Disease Activity Score based on 10 joints (cJADAS10) inactive disease (score <2.5), clinical remission (CID for more than 6 months), and percentage of time spent in CID and cJADAS10 inactive disease.

After 3 years of follow-up, of 297 patients, 190 had started the Step-up plan, 76 the Early Combination, and 31 the Biologic First. At this time, there were no significant differences between the 3 groups in achieving CID and cJADAS10 inactive disease. Nearly 40-60% of pJIA patients failed to achieve both endpoints. However, the proportion of patients who achieved clinical remission and the amount of time patients spent in CID and cJDAS10 inactive disease were significantly higher in the Early Combination group. Indeed, 67.1% of patients in the Early Combination group achieved clinical remission versus 47.3% in the Step-up group. Moreover, the percentage of time in CID for Early Combination patients compared with Step-up patients was 42.1% versus 30.0%. Time in cJADAS10 inactive disease for Early Combination patients compared with Step-up patients was 52.4% versus 40.0%.

"The STOP-JIA study shows that initial therapy and the timing of starting DMARDs is important, even 3 years after treatment initiation," concluded Prof. Kimura. "Overall, the STOP-JIA study showed that pJIA patients are not doing as well as we thought they would. The majority of patients never achieved CID," Prof. Kimura said. In her view, early disease treatment is key to improved outcomes in pJIA.


1. Kimura Y. The Childhood Arthritis and Rheumatology Research Alliance Start Time Optimization of Biologic Therapy in Polyarticular JIA (STOP-JIA) Study: Three-Year Outcomes. 1679, ACR Convergence 2022, 10–14 November, Philadelphia, USA.
2. Ringold S, et al. Arthritis Care Res (Hoboken). 2014;66:1063-72.


# 13. TYK2 inhibition shows potential as a treatment for SLE

**In patients with systemic lupus erythematosus (SLE), deucravacitinib reached its primary endpoint of SLE Responder Index (SRI(4)) with a response rate of 58.2% on a regimen of 3 mg twice daily (BID). The study drug was deemed overall well tolerated.**

The 48-week phase 2 PAISLEY trial (NCT03252587) assessed deucravacitinib as a treatment for patients with moderately to severely active SLE [1]. The study included 363 patients fulfilling inclusion criteria, namely, an SLE Disease Activity Index 2000 (SLEDAI-2K) score ≥6 and ≥1 British Isles Lupus Assessment Group (BILAG) index A or >2 BILAG B manifestations from the musculoskeletal or mucocutaneous domains.

In 4 different study arms, the participants were treated with either placebo or deucravacitinib 3 mg BID, 6 mg BID, or 12 mg once daily (QD). "The patients had to be on stable background therapy, except for glucocorticoids, which were required to be tapered between weeks 8 and 20, and optionally between weeks 32 and 40, and in between those, the steroids needed to be kept stable," Dr Marilyn Pike (MedPharm Consulting, MA, USA) further explained.

At baseline, the mean age of the study cohort was 40.1 years, and 92% were women. The mean SLEDAI-2K was 10.8, the mean count of active joints was 9, and 54.3% had at least 1 BILAG index A.

The results for the primary endpoint of SRI(4) at week 32 were statistically significant for deucravacitinib 3 mg BID and 6 mg BID versus placebo: 58.2% (P=0.0006) and 49.5% (P=0.021) versus 34.4%. "Importantly, the time to response onset was decreased to less than 3 months in the 3 mg BID and not too much greater than that in the 6 mg BID arm compared with placebo," Dr Pike stated. Also, the secondary endpoints of SRI(4) and BILAG-based Composite Lupus Assessment (BICLA) at week 48 demonstrated superiority for deucravacitinib 3 mg BID (57.1% and 47.3%) over placebo (34.4% and 25.6%; P=0.0011 and P=0.0012, respectively). Further

positive results for secondary endpoints were achieved, such as in Lupus Low Disease Activity State (LLDAS) and change in the active joint count. Overall, Dr Pike noted that no added benefit in efficacy was observed by increasing the dose of the study drug.

As for safety, adverse events occurred in 87.8% of those in the placebo arm and between 84.3% and 93.4% in the treatment groups. Serious adverse events were reported in 12.2% in the placebo arm, 7.7% in the deucravacitinib 3 mg BID arm, 7.9% in the 12 mg QD arm, and 8.6% in the 6 mg BID arm. The most common events that occurred in ≥5% of participants were upper respiratory infections, nasopharyngitis, and urinary tract infections.

"We feel that deucravacitinib shows promise as a novel therapy for SLE and warrants further investigation in phase 3 trials," Dr Pike concluded.


1. Pike MC. Efficacy and safety of deucravacitinib, an oral, selective, allosteric TYK2 inhibitor, in patients with active systemic lupus erythematosus: a phase 2, randomized, double-blind, placebo-controlled study. 1117, ACR Convergence 2022, 10–14 November, Philadelphia, USA.


## 14. Belimumab efficacious in cutaneous lupus erythematosus

**A meta-analysis found 44% increased odds of clinical response and an overall response rate of 55% in belimumab users with cutaneous lupus erythematosus. Furthermore, the likelihood of cutaneous flaring was reduced by 49%.**

"As you may know, cutaneous lupus is the most common manifestation of systemic lupus and delays in treatment or inadequate control lead to alopecia, scarring, and permanent pigmentary changes," Dr Daniel Montes (University of Wisconsin, WI, USA) stated as background [1]. He further explained that although belimumab is already approved for systemic lupus erythematosus, knowledge gaps remain.

The presented meta-analysis was undertaken to gain insights into the efficacy of the B-cell activation inhibitor belimumab concerning predominant cutaneous manifestations of lupus and time to therapy response. The primary endpoint looked at clinical response concerning the cutaneous domain of the British Isles Lupus Assessment Group score (BILAG) in patients with or without belimumab. It was defined as a change from BILAG A/B at baseline to BILAG B-E after 52 weeks. "Additionally, we calculated a pooled odds ratio (OR) at each 4-week consecutive interval across 52 weeks to trend the time to clinical response in belimumab users," Dr Montes informed. Based on the PRISMA guidelines, 13 studies were included in the meta-analysis, 6 of them randomised controlled trials.

After 1 year, the likelihood of clinical response in those on belimumab was 44% greater than in non-users (OR 1.44; P<0.0001), while the overall response rate was 55% when also observational studies were comprised. "We noted that the first significant clinical response in belimumab users was at week 20, and this was sustained to week 52, where the peak response was seen," Dr Montes underlined. The OR of having a cutaneous flare was 0.51 (P=0.007), reflecting about half the probability of a flare for belimumab users.

"Our study found that belimumab is an effective biological therapy for patients with cutaneous lupus with or without systemic disease, but it can take up to 20 weeks to achieve a clinically significant response. Thus, belimumab should not be prematurely discontinued," Dr Montes concluded.


1. Montes D. Significant improvement in cutaneous lupus erythematosus with or without systemic lupus erythematosus with belimumab use – a systematic review and meta-analysis. 0348, ACR Convergence 2022, 10–14 November, Philadelphia, USA.


## 15. No increased cancer risk in patients with rheumatic diseases and prior malignancy treated with novel therapies

**A cohort study revealed that cancer risk in patients with rheumatic diseases and a history of previous malignancy did not differ significantly based on the type of biological disease-modifying antirheumatic drugs (DMARDs) and targeted synthetic DMARDs exposure. Besides, there was no difference between those under anti-TNF therapy versus other DMARDs.**

More and more patients with rheumatic diseases are treated with novel therapies, including biological and targeted synthetic DMARDs. Though these patients generally have a higher prevalence of comorbidities, including cancer, available robust data on the malignancy risk is limited.

A cohort study including 352 patients investigated the occurrence and relative risk of incident cancer in those with rheumatic diseases and prior malignancy treated with DMARDs [1]. The study selected patients from the multicentre, prospective Spanish BIOBADASER registry (BIOBADASER 3.0). Records from 9,129 rheumatic patients from 2001 to 2021 were analysed.

Dr Juan Molina Collada (Gregorio Marañón General University Hospital, Spain) and his team defined incident cancer as any cancer

(new primary tumours, local recurrence, or metastases) occurring during drug exposure classified according to Medical Dictionary for Regulatory Activities (MedDRA) and leading to therapy discontinuation.

The study cohort had a mean age of 65.3 years, 70% were female, and had a mean Charlson comorbidity index of 5.2. Overall, 94% (n=331) of the patients had experienced prior non-lymphoproliferative malignancy (solid or melanoma).

"During the study period, we noted 32 incident malignancies, of which 53% (n=17) were solid cancer and 44% (n=14) were non-melanoma skin cancer, whereas 1 patient developed melanoma," Dr Collada said. The overall rate of incident malignancy was 27.1 (95% CI 18.6-38.3) events per 1,000 person-years (PY), ranging between 0 events/1,000 PY in the anti-IL17 group to 51.7 events/1,000 PY in the anti-CTLA-4 group.

The overall rate of incident cancer did not differ significantly in patients exposed to JAK inhibitors (0.6; 95% CI 0.1-2.5), anti-CD20 (0.3; 95% CI 0.1-1.4), anti-IL6 (1.2; 95% CI 0.5-3.4), or anti-CTLA-4 (1.3; 95% CI 0.5-3.6) versus anti-TNF therapy. There was also no difference regarding the rate of different types of cancer (melanoma, non-melanoma skin cancer, or solid tumours) between individual treatment groups compared with anti-TNF.

Besides, the mortality rates in patients exposed to JAK inhibitors, anti-CD20, anti-IL6, anti-IL17, or anti-CTLA-4 versus anti-TNF therapy were similar.

The research team concluded that the risk of incident cancer in patients with rheumatic diseases and previous malignancy did not differ according to the type of DMARDs exposure. Additionally, it did not vary substantially in patients exposed to other DMARDs versus anti-TNF treatment. "We should say that we have not found an increased risk of cancer in this population, although we cannot exclude a potential risk," Dr Collada mentioned. Hence, further long-term registry data is needed to verify these results.

1. Molina J. Risk of cancer after biologic and targeted synthetic DMARDs initiation in patients with rheumatic diseases and a history of prior malignancy: data from the BIOBADASER registry. 0267, ACR Convergence 2022, 10–14 November, Philadelphia, USA.