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# EULAR E-Congress 2020

European League Against Rheumatism

3-6 JUNE 2020

PEER-REVIEWED CONFERENCE REPORT


## Olokizumab shows significant improvements in RA

Results from the phase 3 CREDO-1 trial demonstrated that the novel IL-6 blocker olokizumab significantly improved disease activity and physical function in rheumatoid arthritis patients.

read more on PAGE 4

## axSpA: certolizumab pegol reduces acute anterior uveitis

The phase 4 C-VIEW trial showed significant reductions of AAU flare rate and axial spondyloarthritis disease activity with certolizumab pegol treatment.

read more on PAGE 7

## Fast onset of improvement in PsA with upadacitinib

SELECT-PsA-1: upadacitinib showed fast improvements in musculoskeletal symptoms, psoriasis, physical function, pain, and fatigue and inhibited radiographic progression of patients inadequately responding to non-bDMARD.

read more on PAGE 11

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Editor Prof. Dennis McGongale, University of Leeds, United Kingdom

# Contents



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| | |
|---|---|
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| **ISSN** | 2468-8762 20:6 |





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# Letter from the Editor

**Dear Reader,**

I would like to welcome you to this summary of selected abstracts from EULAR 2020 that captures some key findings that have immediate clinical relevance or that will pique the community interest for further research towards improved patient care. This was the first ever virtual EULAR Congress reflecting the impact of the COVID-19 pandemic on the Global Rheumatology community. The Congress was due to take place in Frankfurt, which is a mere 45km from Mainz where sports terminology such as "heavy metal football" and "geggenpress"(counter press or on the front foot) have emanated and entered popular parlance.

I thought that these terms also applied well to the EULAR 2020 Congress in the context of the current pandemic. Rheumatology certainly had shining past with the Nobel Prize winning discovery of corticosteroids by the Rheumatologist Philip Hench and colleagues but had entered relative obscurity. The COVID-19 pandemic has shown Rheumatology now really is a "heavy metal" speciality with numerous therapeutic agents to treat inflammatory arthritis with these being repurposed and evaluated at the forefront of the COVID-19 battle. We now have a large squad of drugs and continue to acquire drug classes with several examples of these contained in the selected abstracts herein, such as the emergence of JAK inhibition as utility players in inflammatory arthritis and also covers aspects such as specialised drug players with more highly adapted roles in seronegative inflammatory arthritis and lupus.

The Congress also devoted time to dealing with the impact of COVID-19 in subjects taking DMARDS and also exploring the impact of DMARDS on reducing severe inflammation linked to COVID-19 in non-rheumatology patients. The 2020 SARS-CoV2 pandemic with its high inflammation levels linking to mortality and the absence of effective anti-virals has culminated in a rheumatological type "geggenpress" where our legacy drugs are at the forefront on strategies to contain this viral foe.

At the time of writing, corticosteroids have been the big winner in severe COVID-19 pneumonia. However, high-dose steroids in rheumatology patients may be a risk factor for more severe COVID-19. There was one other loser at EULAR 2020 and that was hydroxychloroquine where it failed to show efficacy in a clinical trial in OA, but the door was left open as there may have been an impact on pain. This is not dissimilar to the failure of hydroxychloroquine in COVID-19 pneumonia, although discussions lumbar on. The Rheumatology 2020 therapeutic geggenpress against COVID-19 is still very much in play. However, the EULAR e-congress appears to have been a great success and we, like Mr Klopp, the father of heavy metal football and geggenpressing, should take great solace from our achievements that have also taken place behind closed doors in 2020.

Sincerely,
Prof. Dennis McGonagle

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.

# Rheumatoid Arthritis

## Low DAS at 4 months predicts sustained DMARD-free remission

**Sustained disease-modifying anti-rheumatic drug (DMARD)-free remission (DFR), in this study defined as the absence of clinical arthritis for a minimum of 1 year after stopping DMARD(s), is increasingly achievable in anti-citrullinated protein/peptide antibody (ACPA)-negative and ACPA-positive rheumatoid arthritis (RA) [1,2].**

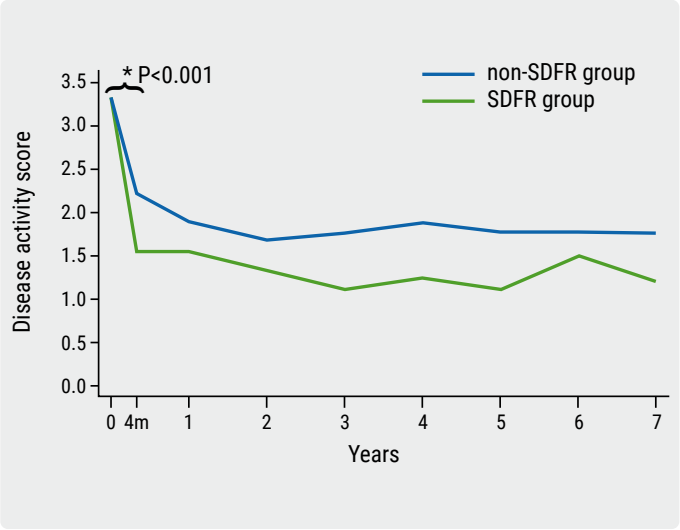
Yet, the pathogenesis underlying sustained DFR-development is unclear; the presence of auto-antibodies, as well as patient characteristics at diagnosis are of importance, but do not exclusively explain sustained DFR [3]. This lack of understanding limits substantiated decisions to discontinue DMARD-treatment in clinical practice.

To gain more insight into sustained DFR in RA, Marloes Verstappen (Leiden University Medical Center, the Netherlands) and colleagues studied the course of disease activity scores (DAS) over time in relation to the development of sustained DFR, and investigated whether the time course of DAS may be helpful to identify patients who are likely to achieve sustained DFR [3]. This study comprised data from 772 RA patients included in the Leiden Early Arthritis Clinic from 1999 onwards. They were treated with initial methotrexate (first choice treatment) and treat-to-target treatment (DAS-steered adjustments from 2005 onwards). Tapering or discontinuation of all DMARDs, including glucocorticosteroids, was done when DAS reached <2.4, in the absence of clinical arthritis. Patients were studied with a median follow-up of 7 years. The primary outcome of the study was sustained DFR. The course of DAS was compared between those who achieved sustained DFR within 7 years and those who did not. This was determined using linear mixed models, stratified for ACPA. Further, the relation was studied between DAS at 4 months and the probability of achieving sustained DFR within 7 years with logistic regression, and Kaplan-Meier curves were generated performed to show the cumulative incidence of sustained DFR for different DAS categories at 4 months (i.e. <1.6, 1.6-2.4, 2.4-3.6, >3.6).

The analysis showed that patients achieving sustained DFR had a remarkably different DAS response within 4 months after diagnosis. Compared with patients who did not achieve sustained DFR, the sustained DFR-group showed a prominently stronger decline in DAS between baseline and 4 months: 1.59 units decline (95% CI 1.24-1.95) versus 0.96 units (95% CI 0.85-1.07) decline (P<0.001) (see Figure). Stratification for ACPA yielded a similar and statistically significant effect in ACPA-negative RA, while in ACPA-positive RA, this effect was absent. In ACPA-negative RA, the probability of achieving sustained DFR during 7 years was lower for patients with higher DAS at 4 months. After 7 years of disease, the cumulative incidence for sustained DFR in ACPA-negative patients with DAS <1.6 at 4 months was high (71.0%), while sustained DFR was rare among those with DAS >3.6 at 4 months (7.1%).

The authors concluded that DAS levels at 4 months are predictive for sustained DFR in ACPA-negative patients, as those with sustained DFR showed a significant stronger DAS decline during the first 4 months after diagnosis. This may mean that the window of opportunity expands to the early phase after diagnosis, and that evaluation of early response

**Figure: Course of DAS over time in relation to sustained DFR achievement in ACPA-negative RA patients [3]**




*Indicates significant stronger decline in DAS in SDFR-group.
ACPA, anti-citrullinated protein antibodies; DAS, disease activity score; SFDR, sustained DMARD-free remission.

to treatment is important in the decision-making to stop DMARDs. The DAS course was not associated with sustained DFR in patients with ACPA-positive RA. Identification and stratification of the ACPA-negative RA subgroups going forward has implications for potentially minimising DMARD exposure.


1. Ajeganova S, et al. Ann Rheum Dis 2015;0:1-2.
2. Verstappen M, et al. RMD open 2020;6(1):e001220.
3. Verstappen M, et al. OP0235. EULAR E-Congress, 3-6 June 2020.


## Olokizumab significantly improves RA features and patient-reported outcomes

**Results from the phase 3 CREDO-1 trial show that treatment with olokizumab over a 24-week period was associated with significant improvements in the signs, symptoms, and physical function of rheumatoid arthritis (RA) as well as in patient-reported outcomes (PROs) in patients with moderate-to-severe RA who previously failed methotrexate therapy [1,2].**

Prof. Rumen Stoilov (University Hospital St. Ivan Rilski, Bulgaria) presented the randomised, placebo-controlled, multicentre, phase 3 CREDO-1 trial that evaluated the efficacy and safety of olokizumab, a new humanised monoclonal antibody targeting interleukin(IL)-6 [3,4]. The trial aimed to evaluate the safety and efficacy of olokizumab 64 mg administered subcutaneously every 2 weeks and 64 mg subcutaneously every 4 weeks versus placebo in the treatment of moderate-to-severe active RA despite treatment with methotrexate. Participants (n=428) received injections of olokizumab 64 mg every 2 weeks (n=143), olokizumab 64 mg every 4 weeks (n=142), or placebo every 2 weeks (n=143) for 24 weeks. After week 24, patients could qualify for an open-label study extension. Primary endpoint of the study was American College of Rheumatology (ACR)20 response at week 12. Secondary endpoints included percentage of patients with low disease activity and improvement of physical ability. Baseline characteristics were comparable between treatment arms.

The results showed that 90.9% of patients in the 2-week dosing group, 94.4% in the 4-week dosing group, and 92.3% in the placebo group completed the study. Both regimens of olokizumab were significantly better than placebo in all primary and secondary endpoints, with 63.6% of patients in the 2-week dosing group and 70.4% of those in the 4-week dosing group achieving ACR20 at week 12 versus 25.9% of patients receiving placebo. The rates for disease activity score (DAS)28 response were 33.6%, 38.7%, and 3.5%, respectively.

Regarding the effect of treatment on quality of Life (QoL), work productivity, and fatigue, the 3 groups were compared for a wide range of PROs, including change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI); Patient Global Assessment of Disease Activity (PtGA); Patient Assessment of Arthritis Pain (Pain); Short Form 36 (SF-36) Physical (PCS) and Mental (MCS) components; European Quality of Life-Five-Dimension Questionnaire (EQ-5D); Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F); and Work Productivity Survey-Rheumatoid Arthritis (WPS-RA) [2]. PRO baseline characteristics were comparable across treatment arms: mean (SD) PtGA was 69.5 (15.5); Pain was 68.6 (17.5); HAQ-DI was 1.7 (0.5); SF-36 PCS was 32.1 (6.5); SF-36 MCS was 42.3 (10.0); EQ-5D was 40.3 (20.0); and FACIT-F was 26.8 (8.7). At week 12, treatment with olokizumab 64 mg every 2 weeks and olokizumab 64 mg every 4 weeks resulted in significant improvement in PRO measures, and these improvements were persistent up to week 24 (see Table).

The incidence of treatment-emergent serious adverse events was numerically higher in the olokizumab groups when compared to placebo, but no unexpected safety signals emerged [1]. The safety profile of olokizumab was

**Table: Patient-reported outcomes change from baseline [2]**

| LSM change from baseline (SE)<br>LSM difference vs placebo<br>97.5% CI for LSM difference | Week 12 | | Week 24 | |
|---|---|---|---|---|
| | Olokizumab q2w (n=143) | Olokizumab q4w (n=142) | Olokizumab q2w (n=143) | Olokizumab q4w (n=142) |
| PtGA | **-30.6** (1.72)<br>-17.5<br>-23.0 to -12.0 | **-31.0** (1.73)<br>-17.9<br>-23.4 to -12.4 | **-32.1** (1.92)<br>-12.7<br>-18.8 to -6.6 | **-36.3** (1.96)<br>-16.8<br>-23.0, -10.6 |
| Pain | **-31.6** (1.82)<br>-18.7<br>-24.6 to -12.9 | **-31.8** (1.83)<br>-19.0<br>-24.8 to -13.1 | **-34.5** (2.05)<br>-13.0<br>-19.5 to -6.5 | **-37.1** (2.08)<br>-15.7<br>-22.3 to -9.1 |
| HAQ-DI† | **-0.54** (0.04)<br>-0.34**<br>-0.47 to -0.21 | **-0.56** (0.04)<br>-0.36**<br>-0.49 to -0.23 | **-0.55** (0.05)<br>-0.27<br>-0.43 to -0.12 | **-0.65** (0.05)<br>-0.37<br>-0.53 to -0.22 |
| SF-36 PCS | **6.72** (0.57)<br>4.53<br>2.72 to 6.33 | **6.03** (0.57)<br>3.84<br>2.01 to 5.67 | **7.84** (0.67)<br>4.30<br>2.19 to 6.41 | **8.73** (0.68)<br>5.20<br>3.04 to 7.35 |
| SF-36 MCS | **6.48** (0.73)<br>3.01<br>0.69 to 5.33 | **7.04** (0.73)<br>3.57<br>1.23 to 5.92 | **6.21** (0.79)<br>3.72<br>1.23 to 6.22 | **8.86** (0.80)<br>6.37<br>3.82 to 8.92 |
| EQ-5D Health Today Score | **19.7** (1.69)<br>12.2<br>6.8 to 17.6 | **18.7** (1.72)<br>11.2<br>5.8 to 16.7 | **20.9** (1.95)<br>12.6<br>6.5 to 18.7 | **23.6** (2.01)<br>15.3<br>8.9 to 21.7 |
| FACIT-F | **8.2** (0.67)<br>4.6<br>2.4 to 6.8 | **8.7** (0.68)<br>5.1<br>2.9 to 7.3 | **8.5** (0.80)<br>4.8<br>2.3 to 7.3 | **10.6** (0.81)<br>6.9<br>4.3 to 9.5 |

* Secondary endpoint; ** P<0.0001. EQ-5D, European Quality of Life-Five-Dimension Question-naire; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; HAQ-DI, Health Assessment Questionnaire-Disability Index; LSM, least square mean; MCS, mental components; PCS, physical components; PtGA, Patient Global Assessment of Disease Activity; SE, standard error; SF-36, Short Form 36; q2w, every 2 weeks; q4w, every 4 weeks.

consistent with what had previously been shown in phase 2 trials with this agent and with data for agents with a similar mechanism of action. At a time when interleukin-6 blockers are in short supply this work highlights the ongoing interest of interleukin-6 antagonism in rheumatoid arthritis.


1. Nasonov E, et al. Abstract OP0021. EULAR E-Congress, 3-6 June 2020.
2. Nasonov E, et al. THU0176. EULAR E-Congress, 3-6 June 2020.
3. Genovese MC, et al. Ann Rheum Dis. 2014;73:1607-1615.
4. Takeuchi T, et al. Mod Rheumatol. 2016;26:473-480.


## New nanoparticle promising future agent in RA

**A first-in-class therapeutic nanoparticle drug for the specific targeting of anti-citrullinated protein antibodies (ACPAs) has been developed, which may be a promising new therapeutic option for patients with rheumatoid arthritis (RA) [1].**

"Several *in vitro* studies have suggested a pathogenic role of ACPAs in RA," according to Prof. Kira Astakhova (Technical University of Denmark, Denmark) who presented the late-breaking abstract. The authors hypothesised that reducing ACPA levels would have a therapeutic effect by blocking cytokine production. Thus, a series of therapeutic nanoparticles for specific targeting of ACPA in synovial fluid was prepared and tested.

Nanoparticles were prepared by the microdroplet method and then decorated with synthetic cyclic citrullinated peptide aptamer PEP2, PEG/hexanoic acid, and fluorophore (Cy5.5). Nanoparticles were used in a series of in vitro assays and in vivo studies including disease activity scores, cytokine measurements, and near-infrared imaging. A fibrinogen-derived 21-amino-acid-long citrullinated peptide with high selectivity toward autoantibodies in RA samples was then identified. Subsequently, this aptamer was incorporated in the chitosan-hyaluronic acid nanoparticle formulation. A fluorescence-activated cell sorting study showed selective uptake of Cy5.5 labelled aptamer-nanoparticle conjugates by neutrophils in the concentration range 0.5-4 nM. No apparent immunogenicity for this nanoparticle formulation was demonstrated, which was in line with results from other trials. A reduction of disease activity of over 50% was achieved in vivo in 3 weeks treatment using as little as 1 nM drug candidate (dosed every 48 hours) in the collagen-induced mouse model of RA (n=30). The same was seen in the serum transfer model (n=10). The aptamer-nanoparticle conjugate significantly reduced interleukin(IL)-6 and tumour necrosis factor (TNF)α levels in the mouse sera. The effects were non-inferior to controls treated with tocilizumab (n=30). The mode of action was then confirmed by applying Cy5.5-labelled aptamer-nanoparticles in the collagen-induced mouse model (n=10). An over 6-fold higher signal accumulation in inflamed versus healthy joints was confirmed; this strongly supports the highly specific nature of the aptamer to the inflammatory process [2]. Given that human RA is characterised by ACPA antibodies preceding disease with distinct kinetics to the animal models reported, it will be interesting to see if these novel strategies will translate in the clinical arena.


1. Khatri S, et al. Abstract LB0002. EULAR E-Congress, 3-6 June 2020.
2. Khatri S, et al. Bioconjug Chem. 2019 Oct 16;30(10):2584-2593.


## Immune-related AEs due to checkpoint inhibitors require care coordination

**Studies have shown that cancer treatment with checkpoint inhibitors can lead to rheumatic and musculoskeletal immune-related adverse events (irAEs), but clear guidance for rheumatologists to manage these events was lacking. An EULAR task force was set up to combine expert opinions on how to manage irAEs without jeopardising the response to the checkpoint inhibitor therapy [1].**

The EULAR task force, consisting of 23 experts, developed 4 over-arching principles and 10 recommendations on the matter [1]. The 4 principles are:

1. irAEs may occur during treatment with checkpoint inhibitors;
2. shared decision-making between patients, oncologists, and rheumatologists is needed;
3. rheumatologists should take an active role in engaging with oncologists when they are managing patients who have musculoskeletal signs and symptoms; and
4. rheumatologists should assist in differential diagnosis and mitigate musculoskeletal symptoms to an acceptable level while enabling effective anti-tumour response in immune checkpoint inhibition.

The resulting 10 recommendations covered a wide spectrum of issues, such as awareness among rheumatologists of the different and varied presentations of irAEs (they can be atypical or have an incomplete presentation) as well as promoting consultation of the rheumatologist by the oncologist when a rheumatic event is first suspected. Symptomatic treatment including non-steroidal anti-inflammatory drugs or analgesics are the initial choice and,

in case of inefficacy, local and/or systemic glucocorticoids should be considered. After glucocorticoids, conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) followed by biologic DMARDs can be used, with tumour necrosis factor (TNF) or interleukin(IL)-6 inhibitors being the recommended biologic agents.

Regarding the use of checkpoint inhibitors, the decision to cease or continue them needs to be based on the severity of irAEs, the extent of immunosuppression that is required to manage them, tumour response, and the future oncology treatment plan. A full rheumatologic assessment was recommended prior to immune checkpoint inhibition. Finally, it was noted that more research, for instance from well-organised trials, is urgently needed as evidence on how to manage irAEs is limited. Also, it must be pointed out that higher doses of corticosteroid used to manage irAEs could potentially impact detrimentally on cancer survival, which is an important consideration for inflammatory arthritis therapy, which poses less of a threat to immediate survival than advanced cancer [2].

1. Benesova K, et al. EULAR E-Congress, 3-6 June 2020.
2. McGonagle D, et al. Autoimmunity Reviews 2020;19(2):102456.

## Preliminary findings suggest rozibafusp alfa effective and tolerable in RA

**For the first time, the safety and tolerability of multiple ascending doses of rozibafusp alfa was reported in patients with rheumatoid arthritis (RA) [1]. An interim analysis of a phase 1b study showed greater numerical improvement from baseline in Patient and Physician Global Assessments of Disease Activity (PtGA and PhGA) compared with placebo, as well as a non-linear, target-mediated disposition.**

Rozibafusp alfa (AMG 570) is a first-in-class bispecific antibody-peptide conjugate targeting T-cell and B-cell activity by inhibiting both the inducible costimulator ligand (ICOSL) and the B cell-activating factor (BAFF). This phase 1b study reported on the safety, pharmacokinetics, pharmacodynamics, immunogenicity, and preliminary efficacy of rozibafusp alfa in RA patients. Enrolled in the study were 34 patients aged between 18 and 75 years with active RA defined as a disease activity score (DAS28-CRP) >2.6. Patients were randomised 3:1 to receive rozibafusp alfa or placebo subcutaneously every 2 weeks for 10 weeks (6 doses) into 4 separate groups of ascending doses of rozibafusp alfa, with 24 weeks of follow-up. All patients were also treated with a stable dose of methotrexate. Primary endpoint of the study was the subject incidence of treatment-emergent adverse events (TEAEs).

The results of the interim analysis show that rozibafusp alfa was generally well tolerated by patients. TEAEs were seen in 92.3% of patients being treated with rozibafusp alfa and in 87.5% of those on placebo. Most of these events were grade ≤2, and the most common TEAE was upper respiratory infection (23.1%) for subjects receiving rozibafusp alfa and nasopharyngitis (37.5%) for subjects receiving placebo. No grade ≥3 treatment-related AEs were observed. Although 11.1% patients who received rozibafusp alfa developed anti-rozibafusp alfa antibodies, there was no correlation to safety or AEs. The preliminary analysis of disease-related activity showed a trend for greater numerical improvement from baseline in PtGA and PhGA with rozibafusp alfa versus placebo in the cohorts receiving the 2 highest doses.

Based on the findings of this trial, further research is underway, with a phase 2, randomised, placebo-controlled study to assess the efficacy and safety of rozibafusp alfa in subjects with active systemic lupus erythematosus (SLE) and inadequate responses to standard-of-care therapy.

1. Abuqayyas L, et al. Abstract FRI0084. EULAR E-Congress, 3-6 June 2020.

# Ankylosing Spondylitis

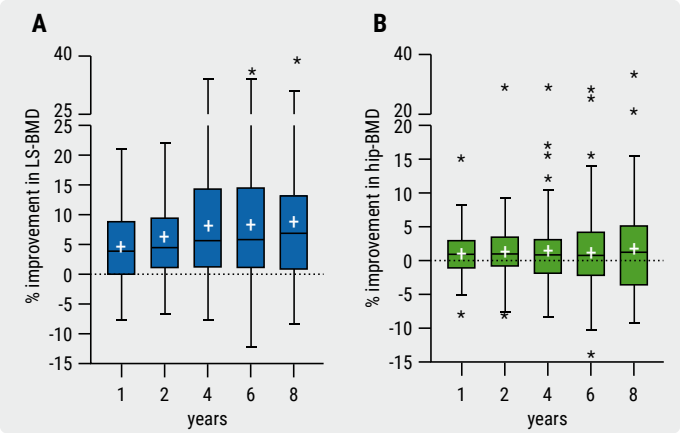
## TNF-α inhibitors improve bone mineral density in AS patients

**Ankylosing spondylitis (AS) patients with longstanding disease achieved significant improvements in both lumbar spine and hip bone mineral density (BMD) during 8 years of tumour necrosis factor (TNF)α blocking therapy [1]. Most pronounced was the effect in the lumbar spine and main improvements occurred during the first 4 years of treatment.**

Bone loss, reflected by low BMD, occurs frequently in patients suffering from AS. Interestingly, it can already be observed at the early stages of the disease. Recent data showed that TNFα blocking therapy has a beneficial effect on BMD, with a 7.2% improvement in lumbar spine BMD and a 2.2% improvement in hip BMD after 4 years of treatment with these agents [2]. Researchers from the Netherlands assessed the effect of 8 years of TNFα blocking therapy on the BMD of the lumbar spine and hip in AS patients. The results of this study were presented by Mark Siderius (University Medical Center Groningen; Medical Center Leeuwarden, the Netherlands).

Of the 131 AS patients included in the study, 73% were male, 83% HLA-B27+, and the mean age was 41.3 years. Patients had received TNFα blocking therapy for at least 8 years, and the use of bisphosphonates at baseline or during follow-up was not permitted. Median symptom duration was 14 years.
During follow-up, which took place at baseline, 1 year, 2 years, and then bi-annually, 27% of patients switched to a second TNFα inhibitor, and disease activity improved significantly during treatment from mean Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-reactive protein (CRP) 3.8 at baseline to 2.1 after 8 years. With regard to BMD, 34% and 19% of patients had low lumbar spine and hip BMD, respectively, at baseline. The BMD of the lumbar spine and hip BMD Z-scores significantly improved during TNFα blocking therapy at all follow-up visits compared to baseline. Significant improvement compared with the previous timepoint was found in the first year, and scores continued to improve up to 4 years of treatment for the lumbar spine and up to 2 years for the hip. Median percentage of improvement in absolute BMD after 8 years of TNFα blocking therapy compared with baseline was 7.1% for the lumbar spine and 1.6% for the hip (see Figure).

**Figure: Bone mineral density improvement in lumbar spine (A) and hip (B) [1]**




BMD, bone mineral density; LS, lumbar spine.
Box-and-whisker plot: Boxes indicate medians with interquartile ranges; + indicates mean; whiskers indicate 1.5 times interquartile distances; * indicate outliers.


1. Siderius M, et al. Abstract THU0376. EULAR E-Congress, 3-6 June 2020.
2. Beek KJ, et al. J Bone Miner Res. 2019;34(6):1041-1048.


## Certolizumab pegol reduces acute anterior uveitis in axial spondyloarthritis

**Results from the ongoing, multicentre, open-label, phase 4 C-VIEW trial show that certolizumab pegol significantly reduces acute anterior uveitis (AAU) flare rate and axial spondyloarthritis (axSpA) disease activity [1].**

AAU is an inflammation of the anterior uveal tract characterised by blurred vision, photophobia, and pain [2]. It is reported in up to 40% of axSpA patients, which makes it the most common extra-articular manifestation in axSpA patients [3]. Previous studies have shown that TNF inhibitor (TNFi) monoclonal antibodies may reduce AAU flare incidence in patients with radiographic axSpA, but data in non-radiographic axSpA is scarce [4-6].

Prof. Irene van der Horst-Bruinsma (Amsterdam University Medical Center, the Netherlands) presented the results of the phase 4 C-VIEW trial that analysed the impact of certolizumab pegol treatment on AAU in patients with active radiographic and non-radiographic axSpA and a recent history of AAU. Eligible patients (n=115) had adult-onset axSpA with ≥3 months symptom duration, active radiographic

or non-radiographic axSpA (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score ≥4 and spinal pain ≥4), inadequate response or contraindication to ≥2 non-steroidal anti-inflammatory drugs (NSAIDs), HLA-B27 positivity, and ≥2 prior AAU flares (with at least 1 flare in the 12 months pre-baseline). Exclusion criteria were any other inflammatory arthritis and prior exposure to >1 TNFi, or primary failure/hypersensitivity to any TNFi.

Participants received certolizumab pegol 400 mg at weeks 0, 2, and 4, then 200 mg every 2 weeks to week 96. The primary variable was incidence of AAU flares compared with historic rates. A pre-specified interim analysis compared AAU incidence in the 48 weeks prior to certolizumab pegol treatment with the 48 weeks of treatment, using Poisson regression adjusted for possible within-patient correlations, with pre- and post-baseline period and axSpA disease duration as covariates. The incidence rates (IR) were calculated based on the number of cases/patients at risk over 48 weeks. Of the 115 participants, 89 initiated certolizumab pegol treatment and 85 patients completed week 48. Mean age of the patients was 46.5 years, 37.1% was female, and 97.8% was Caucasian. The percentage of radiographic axSpA was 85.4%, and 14.6% had non-radiographic axSpA. Mean time since diagnosis was 8.6 years, and mean time since onset of first uveitis flare was 9.9 years. Mean Ankylosing Spondylitis Disease Activity Score (ASDAS) was 3.5 ± 0.9, and mean BASDAI was 6.5 ± 1.5.

Results from this 48-week interim analysis showed that significantly fewer patients had AAU flares during certolizumab pegol treatment than before treatment (IR 0.2 vs 1.5; P<0.001). The number of patients experiencing 1 or ≥2 AAU flares (64.0% and 31.5% at baseline, respectively) was substantially reduced during certolizumab pegol treatment (12.4% and 2.2%, respectively). After 48 weeks of treatment, disease activity improved substantially (mean ± SD ASDAS 2.0 ± 0.9; BASDAI 3.3 ± 2.1); 31.4% of patients achieved ASDAS partial remission and 29.1% ASDAS major improvement.

The authors concluded that 48 weeks of treatment with certolizumab pegol resulted in an 87% reduction in AAU flare rate and substantial improvements in axSpA disease activity, while no new safety signals came to light. These findings suggest certolizumab pegol may be a suitable treatment option for patients with axSpA and a history of recurrent AAU.


1. Van der Horst-Bruinsma I, et al. THU0379. EULAR E-Congress, 3-6 June 2020.
2. Bacchiega ABS, et al. Rheumatology 2017;56:2060-2067.
3. Martin TM, et al. Curr Opin Rheumatol 2002;14:337-341.
4. Van der Heijde D, et al. Rheumatology 2017;56:1498-1509.
5. Van Bentum RE, et al. J Rheumatol. 2019;46:153-159.
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## AxSpA real-life remission rates higher on biologics

**Randomised controlled trials have shown that remission occurs infrequently in axial spondyloarthritis (axSpA) patients treated without biologics [1,2]. Yet, data on remission rates in daily clinical practice are scarce. Thus, Dr Charlotte Baert (Saint Luc University Hospital, Belgium) and colleagues aimed to assess the remission rate in axSpA patients in real life, and to compare the remission rate in axSpA patients on non-steroidal anti-inflammatory drugs (NSAIDs) to the remission rate of those on biologic agents (i.e. tumour necrosis factor [TNF]α blockers or interleukin [IL]-17A blockers) [3].**

This was a cross-sectional study that reviewed clinical data from a single centre (UCLouvain, Belgium) between January 2013 and March 2019, and the last visit available for clinical assessment was evaluated. The analysis included data from 551 axSpA patients of whom 64.3% were male. Disease activity was measured using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and the Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-reactive protein (CRP). Remission was defined as BASDAI <4 and ASDAS <1.3.

In the entire cohort, 478 BASDAI and 317 ASDAS were recorded. The remission rate was 46.7% (n=223) according to BASDAI and 17.3% for ASDAS (n=55). To identify the treatment-related remission rate, patients were stratified by their treatment: NSAIDs (n=285; 62.5% male) or biologics (n=266; 66% male). A total of 245 BASDAI were available for NSAIDs and 233 for biologics. Analysis showed 110 participants on NSAIDs (44.9%) and 113 patients on biologics (48.5%) who were in remission according to BASDAI. ASDAS

**Table: Distribution of ASDAS values in both treatment groups [3]**

| | ASDAS <1.3 | ASDAS ≥1.3 <2.1 | ASDAS ≥2.1 <3.5 | ASDAS >3.5 |
|---|---|---|---|---|
| NSAIDs (n=172) | n=27 (15.7%) | n=41 (23.8%) | n=70 (40.7%) | n=34 (19.8%) |
| Biologics (n=144) | n=28 (19.4%) | n=30 (20.8%) | n=57 (39.6%) | n=29 (20.1%) |

ASDAS, Ankylosing Spondylitis Disease Activity Score; NSAID, non-steroidal anti-inflammatory drugs.

data was available from 172 patients who were treated with NSAIDs and 144 treated with biologics. Of these, 27 (15.7%) and 28 (19.4%) were in remission for NSAIDs and biologics, respectively (P=0.853) (see Table).

The authors concluded that the real-life remission rate in axSpA patients seems to be higher in patients who are treated with biologics. However, compared with NSAIDs the difference is not significant, and many patients treated with NSAIDs achieve remission.


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2. Sieper J. et al. Rheumatology 2016;55(11): 1946-1953.
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## Worse response axSpA patients to second TNFi versus first TNFi

**It has become common practice to start a second tumour necrosis factor inhibitor (TNFi) in patients with axial spondyloarthritis (axSpA) who discontinue their first TNFi [1]. However, evidence on the effectiveness of this strategy in clinical practice has been limited. Moreover, it remains unclear if the reason for discontinuation of the first TNFi influences the response to the second.**

Dr Santiago Rodrigues-Manica (Hospital Egas Moniz, Portugal) and colleagues compared the responses to the first and second TNFi and assessed whether the reason for discontinuation of the first TNFi influences the response to the second TNFi. Data was obtained from the Portuguese ReumaPt registry and included axSpA patients who had discontinued their first TNFi and started a second TNFi and had complete data available on Ankylosing Spondylitis Disease Activity Score (ASDAS) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at baseline, 3 months, and 6 months for their first TNFi. They were then followed every 6 months up to 12 years.

The primary outcome was the ASDAS clinically important improvement (ASDAS-CII). Secondary outcomes included ASDAS major important improvement (ASDAS-MI); ASDAS low disease activity; ASDAS inactive disease (ASDAS-ID); and BASDAI 50. The reason for discontinuation of the first TNFi was defined as: primary failure (i.e. ASDAS-CII was not achieved at 3 or 6 months); secondary failure (i.e. ASDAS-CII achieved at 3 or 6 months but lost in ≥1 follow-up visit); adverse events; or other (e.g. pregnancy, surgery). The response to the first TNFi at 3 and 6 months was compared with the response to the second TNFi at the same visits, adjusting for age, gender, and C-reactive protein (CRP). The association between the reason for discontinuation of the first TNFi and response to the second TNFi over time was tested using generalised estimating equations (GEE) models, adjusted for age, gender, and CRP. Included in the study were 193 patients with a mean age of 45 years, a median follow-up on the second TNFi of 1.5 years; 53% were male.

Patients had a lower response to the second TNFi compared with the first TNFi according to the primary outcome (i.e. ASDAS-CII) at 3 months (41% vs 51%, respectively) and 6 months (35% vs 56%, respectively). An association was observed between the reason for discontinuation of the first TNFi and response to the second TNFi as defined by the most stringent outcomes (ASDAS-MI and ASDAS-ID), but not for ASDAS-CII. Compared with patients who discontinued their first TNFi due to primary failure, patients were more likely to achieve ASDAS-ID with the second TNFi when they discontinued their first TNFi due to secondary failure (odds ratio 7.3; 95% CI 1.9-27.7), adverse events (odds ratio 9.1; 95% CI 2.5-33.3), or other reasons (odds ratio 7.7; 95% CI 1.6-37.9).

Dr Rodrigues-Manica concluded that axSpA patients showed a worse response to the second TNFi compared with the first TNFi. Patients with secondary failure to the first TNFi have a better response to the second TNFi compared with those discontinuing the first TNFi due to primary failure, particularly for most stringent outcomes (i.e. ASDAS-MI and ASDAS-ID). Further, patients with secondary failure to the first TNFi seem to benefit from treatment with a second TNFi. These findings will have implications for studies designed towards selection of second-line therapy in the setting where more drugs are becoming available for axial SpA.


1. Rodrigues-Manica S, et al. FRI0293. EULAR E-Congress, 3-6 June 2020.


## Reduced maintenance dose of certolizumab pegol can be used in axSpA

**Outcomes of the C-OPTIMISE trial show that a reduced maintenance dose of certolizumab pegol may be used in patients with axial spondyloarthritis (axSpA) who have been treated with the drug for a year and who have achieved sustained disease remission, regardless of subpopulation. However, complete treatment withdrawal is not recommended due to the high risk of flares [1,2].**

Prof. Robert Landewé (University of Amsterdam, the Netherlands) presented the multicentre, 2-part, phase 3b

C-OPTIMISE trial. Aim of the study was to determine the number of patients who remained free of disease flare after withdrawal or dose reduction of certolizumab pegol, by analysing whether responses to reduced maintenance dose were comparable in patients stratified by subpopulation, gender, and age. Eligible participants were patients with early axSpA, defined as <5 years symptom duration. Patients were treated with certolizumab pegol 200 mg every 2 weeks with a loading dose of 400 mg at weeks 0, 2, and 4 during the open-label induction period. At week 48, patients in sustained remission (i.e. Ankylosing Spondylitis Disease Activity Score [ASDAS] <1.3 at week 32 or 36 [If ASDAS was <1.3 at week 32, it must be <2.1 at week 36, or vice versa] and at week 48) were randomised to double-blind, full maintenance dose of certolizumab pegol (200 mg every 2 weeks), reduced maintenance dose (200 mg every 4 weeks), or placebo for the maintenance period of 48 weeks. The primary endpoint was the percentage of patients not experiencing a flare (ASDAS ≥2.1 at 2 consecutive visits or >3.5 at any timepoint) between week 48 and 96.

During the 48-week induction period, 43.9% of patients (n=323) achieved sustained remission and 313 patients entered the 48-week maintenance period. During this maintenance period, responses in radiographic and non-radiographic axSpA patients were comparable across all 3 randomised arms. In total, 83.9% of radiographic axSpA patients and 83.3% of non-radiographic axSpA patients who received the full maintenance dose of certolizumab pegol did not experience a flare. This was the case in the reduced maintenance dose arm for 82.1% and 75.5%, respectively. Rates for the placebo group were 17.9% and 22.9%, respectively. Similar responses were seen when stratified by sex or age. Prof. Landewé emphasised that half-dose certolizumab pegol administered after a 48-week induction period is just as beneficial as the full dose, and far better than placebo.


1. Landewé RBM, et al. OP0103. EULAR E-Congress, 3-6 June 2020.
2. Landewé RBM, et al. Ann Rheum Dis. 2020;annrheumdis-2019-216839.


# Psoriasis and Psoriatic Arthritis

## Secukinumab monotherapy as efficient as adalimumab

**Main trial data from the head-to-head EXCEED trial showed that secukinumab monotherapy for biologic-naïve patients with active psoriatic arthritis is at least as efficacious as adalimumab monotherapy and provides higher responses on skin endpoints [1,3].**

The EXCEED trial was a phase 3b study of patients with active psoriatic arthritis and an inadequate response or intolerance to conventional disease-modifying anti-rheumatic drugs (DMARDs). The trial compared the efficacy and safety of secukinumab and adalimumab as first-line biologic monotherapy through 52 weeks, with a musculoskeletal primary endpoint. The results were presented by Prof. Iain McInnes (University of Glasgow, United Kingdom), and simultaneously published in The Lancet [1,2].

Participants (n=853) were randomised to secukinumab 300 mg/week at weeks 0-4 and every 4 weeks thereafter (n=426) or adalimumab 40 mg subcutaneous at baseline and then every 2 weeks until week 50 (n=427). Baseline demographics and disease characteristics were comparable between treatment groups with the exception of higher proportion of female patients and patients without enthesitis in the secukinumab group.

At week 52, American College of Rheumatology (ACR)20 response was achieved by 67.4% of secukinumab-treated patients versus 61.5% of adalimumab-treated patients (P=0.0719). As the primary endpoint was not met, key secondary endpoints were not formally evaluated for statistical significance. However, it was clear that a Psoriasis Area and Severity Index (PASI)90 skin response was achieved by more secukinumab-treated patients than those treated with adalimumab (65% vs 43%, respectively) (see Table).

Table: Efficacy outcomes at week 52 [1]

| Endpoints, % response unless specified otherwise | Secukinumab 300 mg (n=426) | Adalimumab 40 mg (n=427) | P-value (unadjusted) |
|---|---|---|---|
| ACR20 | 67.4 | 61.5 | 0.0719 |
| ACR20* | 66.9 | 59.5 | 0.0239 |
| KEY SECONDARY | | | |
| PASI90** | 65.4 | 43.2 | <0.0001 |
| ACR50 | 49.0 | 44.8 | 0.2251 |
| HAQ-DI mean change from baseline ± SE | -0.58 ± 0.03 | -0.56 ± 0.03 | 0.5465 |
| Resolution of enthesitis (based on LEI) | 60.5 | 54.2 | 0.1498 |
| EXPLORATORY | | | |
| MDA | 43.0 | 37.9 | 0.1498 |
| VLDA | 18.1 | 16.6 | 0.6107 |
| DAPSA LDA+Remission | 61.7 | 53.1 | 0.0178 |
| PASDAS LDA+Remission | 51.1 | 44.1 | 0.0557 |

Binary variables were analysed using logistic regression. Patients who discontinued study treatment prematurely or took csDMARDs after week-36 were considered non-responders. Multiple imputation was used for all other missing data. HAQ-DI mean change from baseline was analysed using mixed-effect model repeated measures.
*Non-responder imputation was used for pre-specified sensitivity analysis
**n=215 in secukinumab and n=202 in adalimumab in psoriasis subset
***n=234 in secukinumab and n=264 in adalimumab in enthesitis subset

Another difference between the groups concerned treatment discontinuation rates (14% with secukinumab vs 24% with adalimumab). The most important reasons for discontinuation were patient or guardian decision, adverse events, and lack of efficacy [1].

Furthermore, a pre-specified subgroup analysis of the trial, presented by Prof. Alice Gottlieb (Mount Sinai Hospital, New York, USA), showed that a higher proportion of patients achieved improvement in combined ACR50 and PASI100 response with secukinumab versus adalimumab (30.7% vs 19.2%, respectively; P=0.0087),adalimumab, as well as in skin specific endpoints (i.e. PASI100 and PASI score ≤3) at week 52 [3]. Higher efficacy was demonstrated for secukinumab compared with adalimumab for PASI100 responses and for the proportion of patients who achieved absolute PASI score ≤3.


1. McInnes IB, et al. OP0227. EULAR E-Congress, 3-6 June 2020.
2. McInnes IB, et al. The Lancet 395;10235:1496-1505.
3. Gottlieb AB, et al. Abstract 0340. EULAR E-Congress, 3-6 June 2020.


## Upadacitinib provides fast onset of improvement in psoriatic arthritis

**Results from the double-blind, randomised-controlled, phase 3 trial SELECT-PsA-1 showed that psoriatic arthritis patients with an inadequate response to ≥1 non-biologic disease-modifying anti-rheumatic drug (non-bDMARD) experienced improvement in musculoskeletal symptoms, psoriasis, physical function, pain, and fatigue and inhibited radiographic progression when treated with upadacitinib. These improvements were seen by week 2, and no new safety signals emerged [1].**

Upadacitinib, an oral, reversible, Janus kinase (JAK) inhibitor approved for the treatment of rheumatoid arthritis, is currently under evaluation for treatment of psoriatic arthritis. The SELECT-PsA-1 study, presented by Prof. Iain McInnes (University of Glasgow, Scotland), assessed the efficacy and safety of upadacitinib compared with placebo and adalimumab in patients with psoriatic arthritis and prior inadequate response or intolerance to ≥1 non-bDMARD.

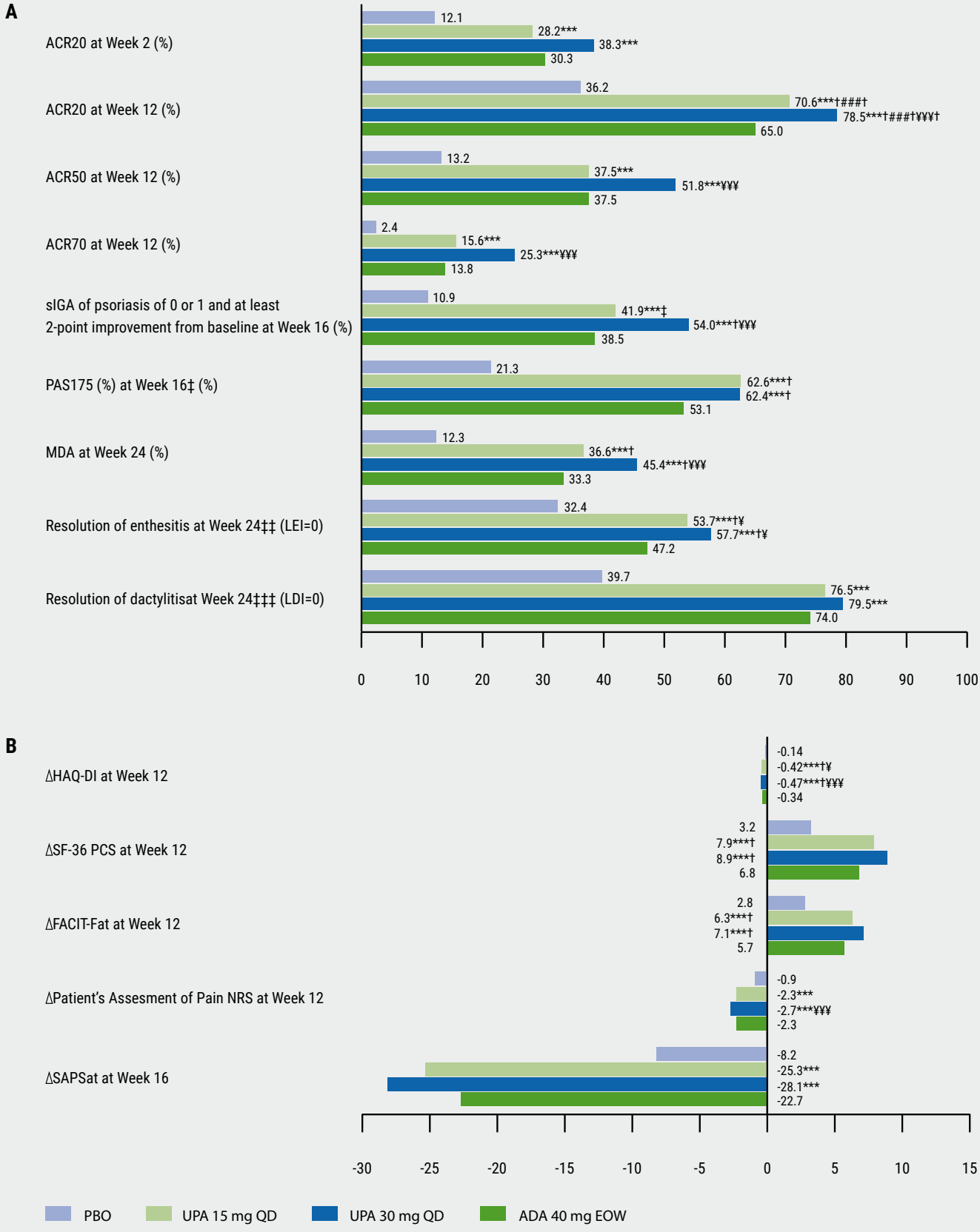
Participants (n=1,704) were randomised to 15 mg upadacitinib once daily, 30 mg upadacitinib once daily, 40 mg adalimumab every other week, or placebo. The primary endpoint of the study was the proportion of patients achieving American College of Rheumatology (ACR)20 for upadacitinib versus placebo at week 12. The mean age of the participants was 50.8 years, 53.2% were female, the mean duration of psoriatic arthritis diagnosis was 6.1 years, and 82% were on ≥1 concomitant non-bDMARD (84% received methotrexate ± another non-bDMARD).

At week 12, ACR20 rates were 70.6% in the 15 mg upadacitinib arm and 78.5% in the 30 mg upadacitinib arm, compared with 36.2% in the placebo group, and 65.0% with 40 mg adalimumab. A greater proportion of patients achieved ACR50/70 with 15 mg or 30 mg upadacitinib compared with placebo, and with 30 mg upadacitinib versus adalimumab (see Figure).

At week 24, change in modified Sharp/van der Heijde score (mTSS) was +0.25 for placebo, -0.04 for 15 mg upadacitinib 15 mg, +0.03 for upadacitinib 30 mg, and +0.01 for adalimumab [1]. Rates of treatment-emergent adverse events (AEs) and serious AEs were similar in the groups receiving placebo, 15 mg upadacitinib, and adalimumab; they were higher in patients receiving 30 mg upadacitinib. However, the safety profile was in line with what was already known from studies of upadacitinib in rheumatoid arthritis.


1. McInnes I, et al. Abstract LB0001. EULAR E-Congress, 3-6 June 2020.

Figure: Efficacy outcomes SELECT-PsA-1 [1]




PBO, placebo: UPA, upadacitinib; ADA, adalimumab; EOW, every other week; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire Disability; LEI, Leeds Enthesitis Index; LDI, Leeds Dactylitis Index; MDA, minimal disease activity; PASI, Psoriasis Area Severity Index; SAPS, Self-Assessment of Psoriasis Symptoms; SF-36, Short Form Health Survey; s-IGA, static Investigator Global Assessment; QD, once daily.
‡ For participants with ≥3% body surface area psoriasis at baseline; ‡‡ for participants with LEI>0; ‡‡‡ for subjects with LDI>0.
*** P<0.001 upadacitinib vs placebo; ** P<0.01 upadacitinib vs placebo; ### P<0.001 for non-inferiority upadacitinib vs adalimumab; ¥¥¥ P<0.001 upadacitinib vs adalimumab; ¥ P<0.05 upadacitinib vs adalimumab.
† Statistically significant in the multiplicity-controlled analysis. Nominal P-value is provided for ACR50/70 at week 12 and ACR20 at week 2.

## Adalimumab added to methotrexate yields better results in PsA than methotrexate escalation

**Results from the ongoing, open-label, phase 4 CONTROL trial shows that adding adalimumab to the treatment regimen of methotrexate results in better outcomes than methotrexate dose escalation in patients with psoriatic arthritis who did not respond sufficiently to initial methotrexate therapy [1].**

The study, presented by Dr Laura Coates (Oxford University, United Kingdom), enrolled 245 biologic-naïve patients with active psoriatic arthritis despite treatment with methotrexate 15 mg every week for at least 4 weeks. Patients were randomised to add-on adalimumab 40 mg every 2 weeks (n=123) or methotrexate dose escalation to a maximum of 20-25 mg/week (n=122; the average dose of methotrexate was 21.8 mg/week).

Baseline characteristics were similar between groups. At week 16, the results showed that 41.5% of patients who were treated with adalimumab achieved minimal disease activity (MDA) compared with 13.1% of patients who received methotrexate escalation treatment. The significantly higher rates of MDA in the adalimumab group occurred irrespective of prior methotrexate treatment duration; rates were 42.2% versus 9.8% for patients treated for up to 3 months and 40.7% versus 16.4% for those treated for a longer period of time. Significant differences in MDA rates between the 2 groups were seen after 4 weeks of treatment. The between-group difference increased with time over the 16-week study period.

The American College of Rheumatology (ACR)20, ACR50, and ACR70 response rates also showed superiority of adalimumab, and significantly higher Psoriasis Area and Severity Index (PASI)75, PASI90, and PASI100 response rates were seen in adalimumab-treated patients who suffered from significant psoriasis compared with those treated with escalated methotrexate. The occurrence of adverse events of any grade was similar in both treatment groups from baseline to week 16 (61.8 vs 57.4% for adalimumab and methotrexate dose-escalation group, respectively). There were no reports of any opportunistic infections, deaths, or tuberculosis or malignancy. The study is currently ongoing and is evaluating whether treatment modification with adalimumab or methotrexate impacts on the achievement and maintenance of MDA.

1. Coates LC, et al. Abstract OP0050. EULAR E-Congress, 3-6 June 2020.

## Ixekizumab shows sustained improvements in pain and fatigue at 3 years

**Patients suffering from psoriatic arthritis often report pain and fatigue. Previous studies have demonstrated improvements in pain and fatigue for up to 2 years with ixekizumab in patients who had an inadequate response or intolerance to tumour necrosis factor inhibitors (TNFi). At the EULAR 2020 meeting, Prof. Ana-Maria Orbai (Johns Hopkins University School of Medicine, USA) presented the 3-year follow-up outcomes of the SPIRIT-P2 trial [1-3].**

The 156-week, phase 3 SPIRIT-P2 study included patients who met the Classification Criteria for Psoriatic Arthritis (CASPAR) and had an inadequate response or intolerance to 1 or 2 TNFi. Although there was a placebo group through week 24, this data was derived only from patients in the intent-to-treat population randomised to ixekizumab at baseline. The 244 participants were randomised to 80 mg subcutaneous ixekizumab every 2 (Q2W; n=123) or 4 weeks (Q4W; n=122) after they received a 160 mg starting dose. Their baseline characteristics are outlined in the Table.

Participants self-rated their symptoms using the Joint Pain Visual Analog Scale (Joint Pain VAS; ranging from 0 [none] to 100 [worst imaginable]), the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36; ranging from 0 [worst] to 100 [best]), and the Fatigue Severity Numeric Rating Scale (Fatigue NRS; 0 [none] to 10 [worst imaginable]). The minimum clinically important difference (MCID) cut-offs were ≥10 for Joint Pain VAS, ≥5 for SF-36 domains, and ≥3 for Fatigue NRS.

**Table: Baseline characteristics [1]**

| | IXE Q4W (n=122) | IXE Q2W (n=123) |
|---|---|---|
| Age, years | 52.6 (13.6) | 51.7 (11.9) |
| Male, n (%) | 63 (51.6) | 50 (40.7) |
| Time since PsA diagnosis, years | 11.0 (9.6) | 9.9 (7.4) |
| Tender joint count (68 joints) | 22.0 (14.1) | 25.0 (17.3) |
| Swollen joint count (66 joints) | 13.1 (11.2) | 13.5 (11.5) |
| Joint Pain VAS, mm | 63.9 (21.4) | 62.7 (20.9) |
| Fatigue NRS | 5.9 (2.5) | 6.0 (2.5) |
| CRP, mg/L | 17.0 (27.5) | 13.5 (26.1) |
| Background cDMARD therapy | | |
| Current use, n (%) | 60 (49.2) | 73 (59.3) |
| MTX, n (%) | 48 (39.3) | 61 (49.6) |
| MTX mean weekly dose, mg | 15.9 (4.8) | 16.0 (4.6) |
| Previous TNFi therapy, n (%) | | |
| Inadequate response to 1 TNFi | 71 (58.2) | 65 (52.8) |
| Inadequate response to 2 TNFi | 41 (33.6) | 46 (37.4) |
| Intolarant to a TNFi | 10 (8.2) | 12 (9.8) |

Mean (standard deviation) unless stated otherwise.

The 156 weeks of treatment was completed by 57.4% of patients in the ixekizumab Q4W group and 44.7% of those in the ixekizumab Q2W group. At week 156, mean change from baseline for the Joint Pain VAS was -28.9 (ixekizumab Q4W) and -25.3 (ixekizumab Q2W). Clinically meaningful improvement of joint pain was reported by 51.8% of patients on ixekizumab (56.1% ixekizumab Q4W and 47.5% ixekizumab Q2W) at week 156. Patients reported an 18-point mean improvement in the SF-36 bodily pain domain. Patients also reported improvements in fatigue up to week 156, with 35.0% of patients achieving the MCID on the Fatigue NRS (39.4% ixekizumab Q4W and 30.6% ixekizumab Q2W). Improvement in fatigue was supported by a 14-point mean improvement in the vitality domain of the SF-36 at week 156.

The researchers concluded that improvements regarding pain and fatigue in patients with psoriatic arthritis with an inadequate response or intolerance to TNFi were sustained through 3 years of ixekizumab treatment in both the Q2W and Q4W treatment groups.


1. Orbai A-M, et al. Abstract FRI0357. EULAR E-Congress, 3-6 June 2020.
2. Kavanaugh A, et al. Clin Exp Rheumatol. 2019;37(4):566-574.
3. Turkiewicz A, et al. Arthritis Rheumatol. 2018;70(S9):2577.


# Osteoporosis and Osteoarthritis

## Positive effect denosumab on fall risk

**Osteoporosis is strongly associated with skeletal muscle dysfunction [1]. A recent study found that treatment with denosumab improved physical performances, grip strength, and gait speed outcomes, and thus appears to reduce the risk of falling for osteoporosis patients.**

Heparan-sulphate proteoglycans are abundant in skeletal muscles and may represent a target for receptor activator of nuclear factor-kB (RANKL) inhibitor, such as denosumab. Thus, Dr Yasser El Miedany (Darent Valley Hospital, United Kingdom) and colleagues set out to investigate the effect of denosumab on fall risk, physical performance, grip strength, and gait speed, and whether a relationship exists with bone mineral density (BMD) [1]. This was done by assessing 127 osteoporotic patients at the start of treatment with denosumab and again after 5 years. The investigators assessed baseline BMD (measured by dual X-ray absorptiometry), the patients' osteoporosis bone profile by means of a blood test, the self-reported Falls Risk Assessment Score (FRAS), the Fracture Risk Assessment Tool (FRAX), and handgrip strength using a calibrated dynamometer (the best of 3 trials of the dynamometer testing was recorded) [2]. The patient's physical performance was assessed by testing for Short Physical Performance Battery (SPPB), Timed Up and Go (TUG), and the 4 Meter Walk Gait Speed. Comparison groups included 112 osteoporosis patients who were treated with zoledronate (once yearly IV injection) for 3 years, and a group of 134 patients who were treated with once weekly oral alendronate 70 mg for 5 years. The patients in both comparison groups were assessed for the same parameters as those who were treated with denosumab. All measures were reassessed 1 year after stopping osteoporosis therapy. No differences were found when comparing the baseline parameters of the 3 groups.

Compared with baseline, a significant increase in BMD was observed in all 3 groups at both the spine and the hip (P=0.02) at 1, 3, and 5 years of denosumab/zoledronate/alendronate treatment, respectively [1]. At 5 years, a significant decrease was observed in the denosumab group in falls risk score (-1.4; 95% CI −2.8 to −0.7; P=0.01), as well as significant improvements in the grip strength (+4.2 kg; P=0.01), SPPB score (+1.2 points; 95% CI−0.07 to 2.2; P=0.02), TUG (+1.7 seconds; 95% CI -2.2 to 0.1; P=0.031), and gait speed (+0.1 m/s; 95% CI 0.03 to 0.2; P=0.01). Zoledronate and alendronate significantly improved the SPPB score (+0.9 and +0.8 points, respectively; P=0.04), TUG (+1.4 and +1.3 seconds, respectively; P=0.05), and gait speed (+0.2 and +0.3 m/s, respectively; P=0.02). No significant change in fall risk was observed (P=0.06 and P=0.07, respectively). One year after stopping treatment with denosumab, researchers noticed a significant worsening of the fall risk score, grip strength, SPPB score, TUG, and gait speed (P=0.1). No difference was seen in all measures 1 year after stopping zoledronate and alendronate. Additionally, no relation was observed to the increase in BMD gained.

Thus, the investigators concluded that denosumab displayed a positive impact and significant improvements in physical performance, grip strength, and gait speed, as well as enhancing multidirectional agility as depicted by TUG. Collectively, this would help explain the reduction of falls risk, which got worse on stopping the medication. Osteoporosis and sarcopenia share similar risk factors, highlighting muscle-bone interactions, which may result in debilitating consequences, such as falls and fractures.


1. El Miedany Y, et al. Abstract OP0313. EULAR E-Congress, 3-6 June 2020.
2. El Miedany Y, et al. J Clin Gerontology and Geriatrics. 2011; 21-26.


## Hydroxychloroquine not effective in patients with hand osteoarthritis

**Data from the first large, randomised, placebo-controlled trial focusing on erosive hand osteoarthritis showed that hydroxychloroquine was no more effective than placebo for changes in pain, function, and radiographic scores in the 52-week period of the study [1].**

Treatment of hand osteoarthritis is complicated as common analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) used for symptomatic relief are often poorly tolerated or contraindicated, especially in elderly patients. At the same time, no effective and proven disease-modifying therapy is available. Dr Claudia Kedor (Charité – Universitätsmedizin Berlin, Germany) presented the results of the randomised, double-blind, placebo controlled, multicentre, investigator-initiated, phase 3 OA-TREAT trial, assessing the efficacy and safety of hydroxychloroquine in patients with inflammatory and erosive hand osteoarthritis.

Patients with inflammatory and erosive hand osteoarthritis were randomised to hydroxychloroquine 200-400 mg per day (n=75) or matching placebo for 52 weeks (n=78). Both groups received standard therapy (stable NSAIDs). The primary endpoint was AUStralian CANadian Osteoarthritis Hand Index (AUSCAN) for pain and hand disability at week 52. The secondary endpoint was radiographic progression from baseline to week 52. Mean age of the patients was 52.4 years in the hydroxychloroquine group and 50.2 years in the placebo group. The percentage of female patients was 90.7% and 76.9%, respectively, and disease duration was 9.5 and 10.8 years, respectively. Baseline pain (AUSCAN) was 31.1 and 30.7, respectively, while baseline function (AUSCAN) was 58.5 and 57.8, respectively.

The results showed that only morning stiffness was significantly reduced in those patients receiving hydroxychloroquine (P=0.001), while changes in radiographic scores did not differ significantly (P>0.05) between both treatment groups (see Table). Regarding safety, 7 serious adverse events were reported in the hydroxychloroquine group versus 15 in the placebo group. No new safety issues were detected. The genesis of stiffness in hand OA could certainly differ from RA and these findings on improvement in stiffness may warrant further investigation.

**Table: ANCOVA-adjusted mean values and 95% CI for primary and secondary outcomes at week 52 [1]**

| Outcome | Adj. Mean HCQ | 95% CI HCQ | | Adj. Mean PBO | 95%-CI PBO | | P-value HCQ x PBO |
|---|---|---|---|---|---|---|---|
| AUSCAN Function | 48.1 | 43 | 53.3 | 51.3 | 46.6 | 56 | 0.36 |
| AUSCAN Pain | 26.7 | 23.9 | 29.4 | 26.5 | 23.9 | 29.1 | 0.92 |
| Tender joint | 6.4 | 4.8 | 7.9 | 7.1 | 5.4 | 8.7 | 0.49 |
| Swollen joint | 2 | 1.3 | 2.7 | 2.1 | 1.4 | 2.7 | 0.93 |
| ESR (mm/h) | 8.2 | 6.9 | 9.6 | 11.7 | 10.1 | 13.5 | <0.01 |
| HAQ | 0.9 | 0.8 | 1 | 0.8 | 0.7 | 0.9 | 0.46 |
| Phys. Global | 3.2 | 2.8 | 3.6 | 3.5 | 3 | 3.9 | 0.39 |
| Pat. Global | 4.5 | 3.9 | 5.1 | 5.2 | 4.6 | 5.8 | 0.14 |
| SF36 mental | 48.8 | 46.6 | 51 | 50.8 | 48.7 | 52.8 | 0.22 |
| SF36 physical | 39.8 | 38 | 41.6 | 39.9 | 38.2 | 41.6 | 0.95 |
| Morning Stiffness (min) | 30.2 | 24 | 36.3 | 16.3 | 10.3 | 22.3 | 0.001 |
| Modif. Kallmann Score | 53.6 | 52.1 | 55.1 | 52.8 | 51.4 | 54.2 | 0.24 |

The associated baseline value or, if available, a mean value from baseline and screening was included in the ANCOVA model as a covariate.


1. Kedor C, et al. Abstract OP0186. EULAR E-Congress, 3-6 June 2020.


## Higher mortality risk with tramadol versus NSAIDs for osteoarthritis patients

**A recent study showed that osteoarthritis patients treated with tramadol have an increased risk of all-cause mortality, cardiovascular disease (CVD), venous thromboembolism (VTE), and hip fracture within 1 year compared with NSAIDs. No statistically significant difference was observed between tramadol and codeine [1].**

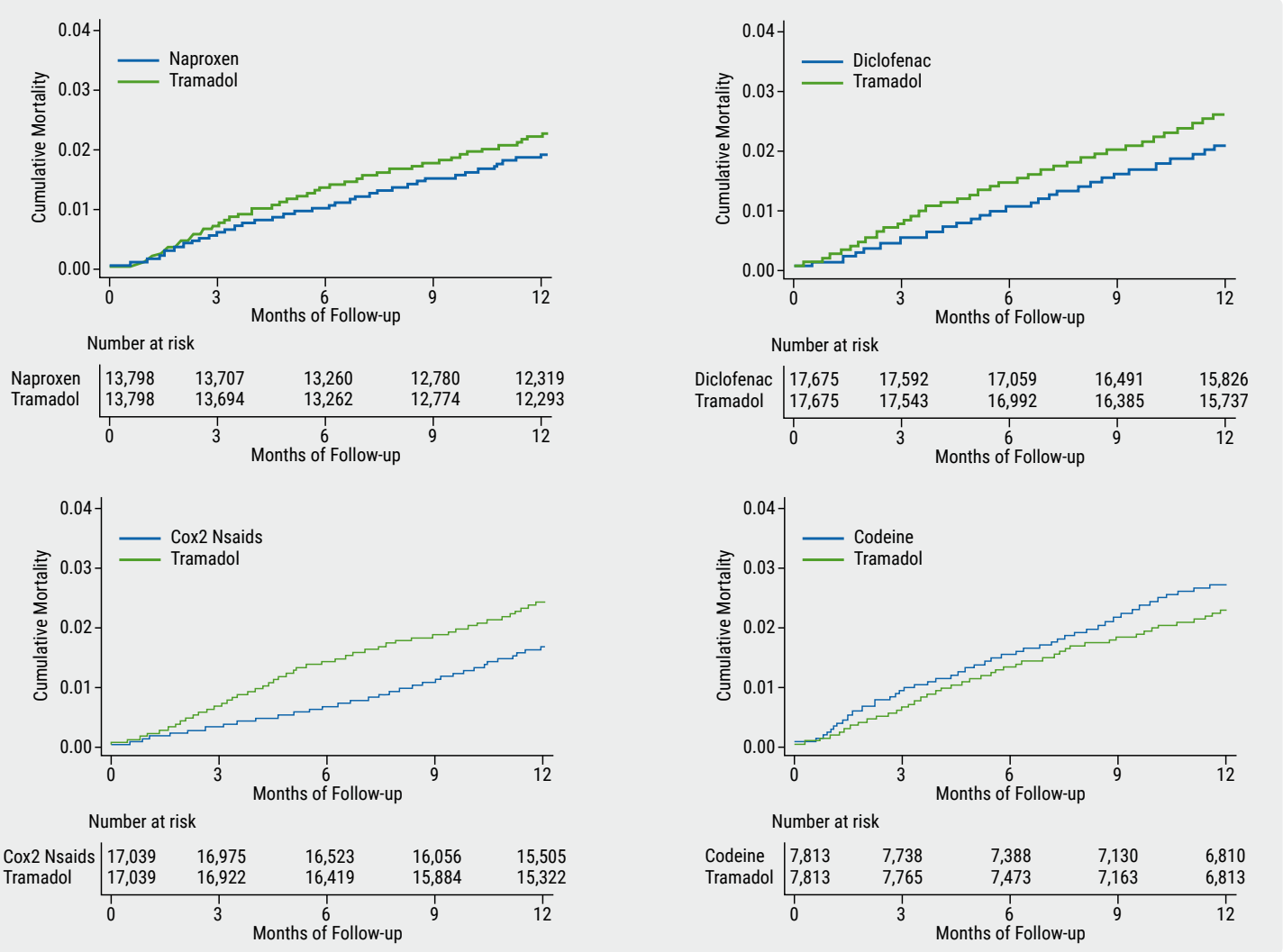
Both tramadol and non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for pain relief in osteoarthritis patients. However, the evidence comparing the risks of adverse events between tramadol and NSAIDs users has been inconclusive. Thus, Lingyi Li (University of British Columbia, Canada) and colleagues assessed the association of tramadol with all-cause mortality, CVD, VTE, and hip fractures compared with NSAIDs and codeine in osteoarthritis patients.

This was done in a sequential propensity score-matched cohort study. Eligible participants were osteoarthritis patients who received medical care from 2005 to 2014 in the province of British Columbia, Canada. The tramadol cohort included 56,325 patients who had an initial prescription of tramadol. The 4 comparator cohorts included patients who had initiated one of the following: naproxen (n=13,798), diclofenac (n=17,675), cyclooxygenase-2 [Cox-2] inhibitor (n=17,039), or codeine (n=7,813). Participants required to be prescribed neither tramadol nor its comparators during the year prior to the initial prescription date. Outcomes were all-cause mortality; first ever CVD, VTE, and hip fracture within 1 year after the initiation of tramadol or its comparators. Patients were followed-up from index date until the event occurred, disenrollment, or the end of a 1-year follow-up period. After propensity score matching, a total of 112,650 patients with osteoarthritis were included (mean age of 68 years; 62.8% was female).

During the 1-year follow-up, 296 deaths (21.5/1,000 person-years) occurred in the tramadol cohort and 246 (17.8/1,000 person-years) in the naproxen cohort. Patients with osteoarthritis who were treated with tramadol had a 20-50% higher risk of death during the first year of treatment than patients who were treated with NSAIDs, but no significant difference was observed compared with the codeine cohort. Compared with the NSAIDs cohort, patients treated with tramadol also had an increased risk of CVD, VTE, and hip fracture (see Figure). The impact of pain severity as a factor necessitating tramadol prescription and potential confounders associated with this including reduced mobility as potentially relevant mechanisms merits further considerations.

1. Li L, et al. Abstract OP0191. EULAR E-Congress, 3-6 June 2020.

**Figure: Outcomes on mortality [1]**



# Systemic Sclerosis and Systemic Lupus Erythematosus

## Composite endpoint CRESS for primary Sjogren's syndrome

**A concept has been developed for a new composite endpoint for primary Sjögren syndrome trials [1]. The 'Composite of Relevant Endpoints for Sjogren's Syndrome' (CRESS) might better suit the heterogenous nature of Sjogren's syndrome than a single primary endpoint and is able to discriminate between abatacept and placebo response in patients with this condition [1]. Additional validation analyses in independent, global, multicentre, placebo-controlled trials of biological disease-modifying anti-rheumatic drugs (DMARDs) will be performed.**

Dr Suzanne Arends (University Medical Center Groningen, the Netherlands) and colleagues aimed to develop a composite endpoint for primary Sjogren's syndrome based on expert opinion and analysis of trial data. The CRESS endpoint consists of 5 items that were identified by experts as the most relevant aspects to assess the effect of treatment in primary Sjogren's syndrome patients:

1. systemic disease activity: EULAR Sjogren's syndrome disease activity index (ESSDAI);
2. patient-reported symptoms: EULAR Sjogren's syndrome patient-reported index (ESSPRI);
3. tear-gland function: ocular staining score (OSS);
4. salivary gland function: stimulated whole saliva (SWS); and
5. serological items: rheumatoid factor/immunoglobulin G (RF/IgG).

Dr Arends and colleagues tested these 5 items using data from the randomised, double-blind, placebo-controlled ASAP-III trial, assessing safety and efficacy of abatacept (n=40) versus placebo (n=39) at week 25 [2]. For each item, ROC analysis was used to assess the discrimination of effect between the ASAP-III treatment groups, with optimal cut-off point being defined by the highest sum of sensitivity and specificity. For ESSDAI, ROC analysis showed that both absolute and relative change were not able to discriminate between treatment groups (AUC 0.536 and 0.559, respectively) and no optimal cut-off point could be identified. According to an endpoint developed in systemic lupus erythematosus [3] and based on expert opinion, it was decided to maintain the validated cut-off for low disease activity (ESSDAI <5) [3]. For ESSPRI, ROC analysis (AUC 0.629) showed an optimal cut-off point of -13.8% and the validated cut-off for ESSPRI response was used (decrease ≥15% or ≥1 point) [3]. For OSS and SWS, again ROC analysis (AUC 0.555 for OSS >3 at baseline and AUC 0.556 for SWS >0 at baseline) could not identify optimal cut-off points, so the definitions based on expert opinion were kept. For the serological items, ROC analysis (AUC 0.861 for RF >0 at baseline and 0.615 for IgG) showed optimal cut-off points of -23% and -2.2%, respectively. These numbers were rounded to a decrease ≥25% in RF or a decrease ≥5% in IgG.

Taken together in CRESS, response to ≥3 of the 5 listed items discriminated best between the abatacept and placebo groups. The final response rate to the composite endpoint (CRESS responders) in ASAP-III was 55% versus 13% in the abatacept and placebo groups, respectively. The findings of this comparatively small study need validation in a larger cohort.


1. Arends S, et al. Abstract OP0186. EULAR E-Congress, 3-6 June 2020.
2. Van Nimwegen JF, et al. Lancet Rheumatol 2020;2(3):e153-E163.
3. Seror R, et al. Ann Rheum Dis. 2016;75(2):382-9.

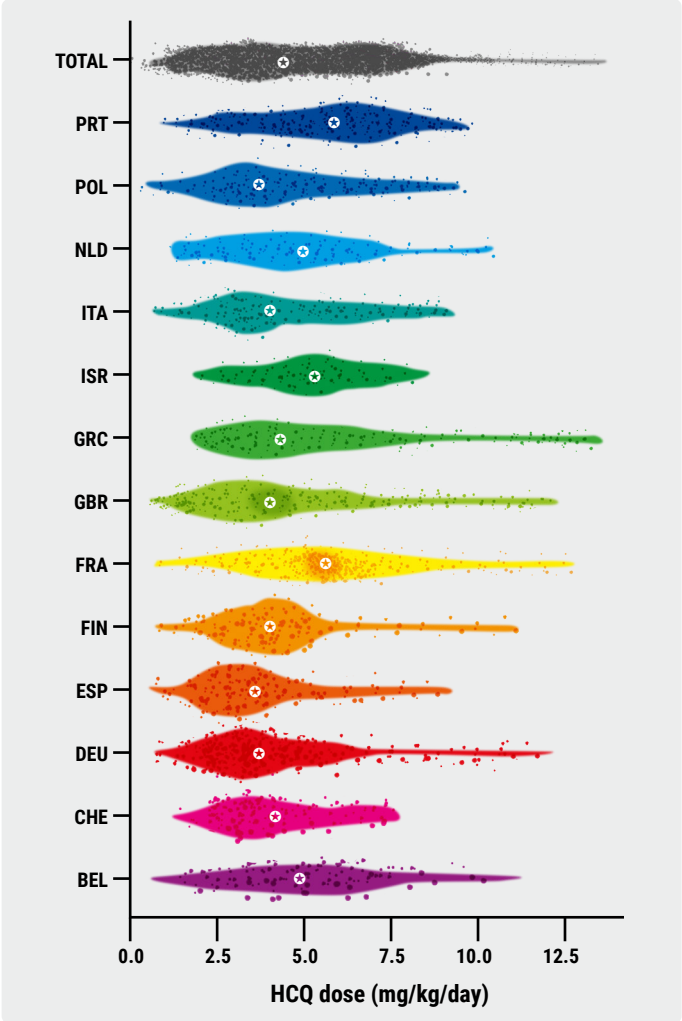

## Wide variation in prescription and dosing patterns for hydroxychloroquine in SLE

**EULAR guidelines concerning long-term use of hydroxychloroquine in systemic lupus erythematosus (SLE), recommending a maximum dose of 5 mg/kg/day and ophthalmological screening at baseline and annually after 5 years of hydroxychloroquine treatment [1], have already affected its prescription patterns in Europe [2]. However, there are large inter- and intra-country variations of hydroxychloroquine dosing. Notably, most centres fail to follow recommendations regarding annual screening of retinopathy in case of long-term hydroxychloroquine use.**

Although the long-term use of hydroxychloroquine is very common in patients with SLE, it may come with certain adverse effects such as the development of hydroxychloroquine retinopathy, especially in case of very long-term use (>5 years) and at high doses (>5 mg/kg/day) [3,4]. In 2019, EULAR guidelines addressed this issue by recommending a maximum hydroxychloroquine dose of 5 mg/kg/day and ophthalmological screening at baseline and annually after 5 years of hydroxychloroquine treatment when used in the management of SLE [1]. Zgjim Osmani and colleagues (National Association for Lupus, APS, Scleroderma and MCTD, the Netherlands) assessed whether these EULAR guidelines affected prescription patterns and screening frequencies in Europe.

Data was collected from the online European Survey for Lupus Patients (ESLP) initiated by LUPUS EUROPE online.

**Figure: Median hydroxychloroquine dosages in Europe [2]**




PRT: Portugal, POL: Poland, NLD: Netherlands, ITA: Italy, ISR: Israel, GRC: Greece, FRA: France, FIN: Finland, ESP: Spain, DEU: Germany, CHE: Switzerland, BEL: Belgium.

European patients were offered the opportunity to take part, and to complete 29 questions. Each participant was asked, among other things, to report their body weight, daily hydroxychloroquine dose, and whether they had received baseline screening and/or regular eye examinations. This online survey was completed by 2,938 lupus patients from 36 countries. The majority were female (86.5%) and 85.7% was diagnosed with SLE. Data on the daily hydroxychloroquine dose was available from 57.1% of patients (n=1,678), with a median dose of 4.3 mg/kg/day and a median treatment duration of 7 years.

It emerged that 36.8% of patients exceeded the recommended daily dose of 5 mg/kg/day. Low dose (≤4 mg/kg/day) was reported by 45.8% (n=769). The percentage of patients reporting that they skipped hydroxychloroquine once a week or more often was 15.9% (n=284). Nevertheless, only 8.7% of patients reported that they were more likely to skip hydroxychloroquine than other medication. The highest median hydroxychloroquine dosages were reported by patients from Belgium, Israel, France, and Portugal, whereas Spanish patients reported the lowest hydroxychloroquine dosages (see Figure).

Furthermore, 82.2% of patients (n=935) who were diagnosed in the past 10 years reported that they received an ophthalmological screening at baseline. Of the 39.7% of patients (n=1,167) who reported long-term use of hydroxychloroquine (i.e. ≥ 5 years), only 64% (n=748) reported that they receive regular eye examinations (i.e. at least once every year). It was stated that these outcomes offer interesting insights into the different practices amongst European countries, and that more research is needed to confirm whether proper screening modalities are being employed as recommended.


1. Fanouriakis A, et al. Ann Rheum Dis. 2019 Jun;78(6):736-745.
2. Osmani Z, et al. Abstract SAT0169. EULAR E-Congress, 3-6 June 2020.
3. Jorge A, et al. Nat Rev Rheumatol. 2018 Dec;14(12):693-703.
4. Marmor MF, et al. Ophthalmology. 2016;123(6):P1386-94.


## Subclinical myocardial involvement progresses in SSc patients

**Dr Devis Benfaremo (Università Politecnica delle Marche, Italy) described the progression of myocardial deformation in patients with systemic sclerosis (SSc) and no overt cardiac disease and found that global longitudinal strain (GLS) impairment progressed over a 20-month follow-up period in these patients [1].**

This was the main finding of an Italian prospective longitudinal study, which included 72 SSc patients (68 female, mean age 56.6 years) who fulfilled the 2013 ACR/EULAR classification criteria for SSc. Patients with structural heart disease, heart failure, atrial fibrillation, or pulmonary hypertension were excluded from the study. An echocardiographic examination was performed for all patients at baseline and during their follow-up evaluation. Standard and speckle-tracking derived variables, including GLS, were acquired to assess systolic and diastolic function of the left (LV) and right ventricle (RV). Additional recorded data consisted of disease subset, antibodies pattern, cardiovascular risk factors, and involvement of other organ systems.

Common echocardiographic parameters of left and right systolic function were within normal range at baseline and did not change during follow-up. Mean GLS, however, worsened for both LV (from -19.8 ± 3.5% to -18.7 ± 3.5%; P=0.034) and RV (from -20.9 ± 6.1% to -18.7 ± 5.4%; P=0.013) during a median follow-up of 20 months. The increased GLS impairment registered in SSc patients was homogenous across endocardial, mesocardial, and epicardial layers of both ventricles, as well as myocardial segments. There was no difference in GLS impairment progression rate when patients were stratified according to disease subset or other clinical parameters. Dr Benfaremo urged that more studies are needed to assess the significance of subclinical heart involvement and its progression in patients with SSc.

1. Benfaremo D, et al. Abstract SAT0307. EULAR E-Congress, 3-6 June 2020.

## Anifrolumab achieves rapid and durable BICLA-response

**Data from the phase 3 TULIP studies showed that treatment of systemic lupus erythematosus (SLE) patients with anifrolumab resulted in more British Isles Lupus Assessment Group (BILAG)-based Combined Lupus Assessment (BICLA) responses compared with placebo, starting at early timepoints and being sustained through week 52. Prof. Eric Morand (Monash University, Australia) who presented these studies, stated that rapid and durable BICLA response supports the clinical benefit of anifrolumab for patients with moderately to severely active SLE [1].**

The human monoclonal antibody anifrolumab is a type I interferon (IFN) receptor antagonist, which has previously shown promising results in the phase 3 TULIP-2 and TULIP-1 trials in SLE [2,3]. Both TULIP-2 (anifrolumab n=180; placebo n=182) and TULIP-1 (anifrolumab n=180; placebo n=184) were randomised, double-blind, placebo-controlled trials which evaluated the efficacy and safety of anifrolumab (300 mg every 4 weeks) over 52 weeks in patients with moderately to severely active SLE who were receiving standard-of-care treatment [2,3]. BICLA responses on anifrolumab versus placebo at week 52 showed differences of 16.3% (95% CI 6.3-26.3; P=0.001; primary endpoint) and 16.4% (95% CI 6.7–26.2; secondary endpoint), respectively. However, optimal attributes of therapeutics for SLE include rapid onset and durability of response.

In this follow-up study, Morand et al. compared BICLA responses on anifrolumab versus placebo over time in both TULIP studies, and pooled data for early timepoints, for time to onset of BICLA response sustained to week 52, as well as for major and partial clinical response [1]. BICLA response was defined as all of the following: 1) reduction of baseline BILAG-2004 domain by at least 1 gradation and no worsening in other BILAG-2004 organ systems; 2) no worsening of disease activity (determined by SLE Disease Activity Index (SLEDAI)-2K and Physician Global Assessment (PGA); 3) no study treatment discontinuation; 4) no use of restricted medications beyond protocol-allowed thresholds [2,3]. Major clinical response was defined as all BILAG-2004 scores C or better at week 24, maintained through week 52, with no new A or B scores between weeks 24-52, whilst partial clinical response was defined as a maximum of 1 BILAG-2004 B score at week 24, maintained through week 52, with no new B domain scores through week 52. The majority of patients was young (median age pooled from both studies 42.6 years) and female (92.5%).

Results showed that at the first 3 assessments in TULIP-2 (at weeks 4, 8, and 12), numerically higher percentages of patients treated with anifrolumab (26.8%, 35.3%, and 42.9%, respectively) were classified as having a BICLA response compared with patients receiving placebo (21.3%, 21.6%, and 31.8%). A similar trend was observed in TULIP-1 with anifrolumab (23.3%, 34.2%, and 36.5%) versus placebo (18.3%, 23.2%, and 27.5%). The time to onset of BICLA response sustained through week 52 favoured anifrolumab in both TULIP-2 (HR 1.55; 95% CI 1.11-2.18) and TULIP-1 (HR 1.94; 95% CI 1.38-2.73). These data translate into an HR of 1.73 (95% CI 1.37-2.20) for the pooled data. In TULIP-2, 86 (47.8%) patients treated with anifrolumab had BICLA responses that were sustained through week 52 compared

with 57 (31.3%) patients in the placebo group. Major clinical response was achieved by 22.1% of anifrolumab patients in TULIP-1 versus 15.8% of those on placebo, and 20.8% versus 10.9% in TULIP-2; pooled data showed a major clinical response rate of 21.5% for anifrolumab versus 13.4% for placebo. Partial clinical response was achieved in 45.4% of anifrolumab patients in TULIP-1 versus 40.2% of placebo patients, 46.8% versus 38.4% in TULIP-2, and 46.1% versus 39.3% in the pooled data. It was concluded that anifrolumab not only achieved more BICLA responders compared with placebo, but that the time of onset favoured anifrolumab as well.


1. Morand EF, et al. Abstract P0003. EULAR E-Congress, 3-6 June 2020.
2. Morand EF, et al. N Engl J Med. 2020;382:211–221.
3. Furie RA, et al. Lancet Rheumatol. 2019;1:e208–e219.


# COVID-19

**Undoubtedly highly anticipated during this year's EULAR were the updates and recommendations concerning COVID-19. In a joint effort, experts aimed to gather the latest insights and solutions to the global pandemic.**

## COVID-19 and inflammatory rheumatic disease: some key issues

**The currently available data suggests that patients with inflammatory rheumatic conditions do not exhibit an increased frequency of COVID-19 infection or a more severe course of the disease in general. General risk factors –such as older age, obesity, cardiovascular conditions, chronic lung conditions, hypertension, and diabetes– seem to be much more important in this respect.**

During a unique virtual press conference, Prof. Gerd Burmester (EULAR Public Affairs Officer; Charité University Hospital, Germany) addressed some issues regarding medication, inflammatory rheumatic disease, and COVID-19 infection [1]. He emphasised that discontinuing immunomodulatory medication is not a good idea, as patients with inflammatory rheumatic diseases do not have an increased frequency of infection with COVID-19, nor do they experience a more severe course of the infection. Moreover, stopping therapy may trigger a relapse of the disease, which may lead to an unfavourable immunological situation or subsequent increased administration of cortisone, which has its specific hazards.

Prof. Burmester subsequently debunked the myth on the use of hydroxychloroquine in COVID-19 prevention or treatment, stating that either some studies that investigated the drug were uncontrolled or participants were given the drug with concomitant medication. Also, hydroxychloroquine was administered in patients with pre-existing conditions and cardiovascular comorbidities; these results can therefore not be transferred to the common situations when treating autoimmune disorders. Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, were initially thought to pose a danger to patients with COVID-19, but this has found not to be the case. Thus, NSAIDs can continue to be used.

Similarly, it is important to know that angiotensin-converting enzyme (ACE) inhibitors, which are frequently used to treat hypertension for patients with a condition such as rheumatoid arthritis, are safe for patients infected with COVID-19. Moreover, current discussion focuses on a potential beneficial effect of these drugs on this condition.

Prof. John Isaacs (Newcastle University, United Kingdom) addressed the increased risk for COVID-19 in rheumatic patients who are suffering from venous thromboembolism (VTE). The reason that COVID-19 patients are susceptible to VTE may be related to the inflammation as well as the fact that the virus may infect the endothelium of the blood vessels. As it is known that antirheumatic drugs such as tumour necrosis factor (TNF)α inhibiting drugs, interleukin (IL)-6 blockers, and Janus kinase (JAK) inhibitors reduce thrombotic risk by lowering inflammation, they are being studied in hyperinflammation in COVID-19 and may be able to reduce the side effects of the disease, according to Prof. Isaacs [2].

Reassurance about recovery from COVID 19 was at hand from Prof. Pedro Machado (University College London, United Kingdom), who conducted a study assessing rheumatic patients or those with musculoskeletal diseases who had been infected with COVID-19: "Most of them recover from the virus, regardless of which medication they receive for their rheumatic condition." In total, 600 COVID-19 patients from 40 countries were included in the study; 46% of patients were hospitalised and 9% died. Those who were treated with TNF inhibitors were found to be less likely to be hospitalised for COVID-19 (odds ratio [OR] 0.40; 95% CI 0.19-0.81). Contrary, prednisone dose ≥10 mg/day was associated with higher odds of hospitalisation (OR 2.05; 95% CI 1.06-3.96). The use of conventional disease-modifying anti-rheumatic drugs (DMARDs) alone or in combination with biologics/JAK inhibitors was not associated with hospitalisation (OR 1.23; 95% CI 0.70-2.17 and OR 0.74; 95% CI 0.37-1.46, respectively). Neither NSAID use or anti-malarial use were associated with hospitalisation status (OR 0.64; 95% CI 0.39-1.06 and OR 0.94, 95% CI 0.57-1.57, respectively) [3].

### Recommendations for managing rheumatic and musculoskeletal diseases in the COVID-19 era

A set of recommendations on the management of patients with rheumatic and musculoskeletal diseases has been developed by EULAR [4]. These recommendations focus on prevention of COVID-19; managing patients in general; and managing patients who have been infected or have been in contact with a COVID-19 patient. The recommendations were simultaneously published in the Annals of the Rheumatic Diseases [5]. Despite the sparse evidence combined with the tremendous time pressure under which these recommendations were made, EULAR was able to develop a preliminary set of recommendations on the management of patients with rheumatic and musculoskeletal diseases in the COVID-19 era. Prof. Robert Landewé (Academic Medical Center Amsterdam and Zuyderland Medical Center Heerlen, the Netherlands) emphasised that they are indeed preliminary and that updates are eagerly awaited. "However, for the time being, it will have to do." The 13 recommendations are based on 4 themes outlined in the Table [4,5].

**Table: The 4 themes on which the EULAR recommendations for COVID-19 are based [4,5]**

| | |
|---|---|
| **General matters of prevention of COVID-19** | ◆ Key to prevent spreading of the virus are:<br>• washing hands<br>• mask-wearing<br>• social distancing |
| **Managing patients during the COVID-19 pandemic** | ◆ Patients with rheumatic disease who have symptoms of COVID-19 should be tested<br>◆ Treatment for their chronic condition should continue<br>◆ Consultation should take place via telehealth unless there is absolute urgency for an in-person consultation |
| **Managing patients who have been in contact with COVID-19 patients or who have contracted the virus themselves** | ◆ The vast majority of people who are infected with COVID-19 are asymptomatic or have mild disease<br>• No need to go to the doctor or hospital<br>• Up to the patient and physician to decide on this<br>◆ Do patients have symptoms of more severe COVID-19 disease and/or are their symptoms rapidly worsening?<br>• Referral to an intensivist, infectious diseases specialist or pulmonologist necessary |
| **Pulmonary complications** | ◆ Doctors should be aware of this<br>• Patients should be to a pulmonologist when they think this is the case. |

Full recommendations can be found online.

**Editors Note:** In a fast-changing evolving field, the UK OpenSAFELY cohort of 17 million records has since showed a very marginal increased mortality in RA/SLE/psoriasis combined groups compared with a 50-59-year-old reference group [6]. Secondly, pulmonary immunothrombosis secondary to viral alveolitis rather than active pulmonary endothelialitis appears to be a key mechanism of thrombosis given the reported efficacy of corticosteroids from the RECOVERY trial [7,8].


1. Burmester GR. EULAR E-Congress, 3-6 June 2020.
2. Isaacs J. COVID-19 - an update. EULAR E-Congress, 3-6 June 2020.
3. Gianfrancesco M, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry.
4. Landewé RBM. Provisional recommendations COVID-19. EULAR COVID-19 Recommendations. EULAR E-Congress, 3-6 June 2020.
5. Landewé RBM, et al. EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. Ann Rheum Dis. 2020;annrheumdis-2020-217877.
6. Williamson EJ, et al. Nature 2020. Doi:10.1038/s41586-020-2521-4.
7. McGonagle D, et al. The Lancet Rheumatology 2020;2(7):E437-E445.
8. RECOVERY Collaborative Group. N Engl J Med. 2020. DOI: 10.1056/NEJMoa2021436.