Medicom International Conference Series in Rheumatology

EULAR 2021 Virtual Congress

European Alliance of Associations for Rheumatology

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PEER-REVIEWED CONFERENCE REPORT

COVID-19 Vaccines in Rheumatic Disease

Several DMARDs undermine the immunogenicity of COVID-19 vaccines in patients with rheumatic disease. Nonetheless, the vaccines are safe and well tolerated in these patients.

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COSMOS: Guselkumab Efficacious in PsA

COSMOS is the first study to assess an IL-23 inhibitor specifically in patients with PsA who failed prior TNF inhibitor treatment. Guselkumab was safe and efficacious in this patient population.

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JUNIPERA: Secukinumab in Juvenile Idiopathic Arthritis

Secukinumab was efficient and safe in children with enthesitis-related arthritis and juvenile psoriatic arthritis, as shown in the phase 3 JUNIPERA trial.

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

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Letter from the Editor

Prof. Dennis McGonagle

Dear colleagues,

The EULAR 2021 Congress was again an E-congress that was originally planned for Paris in the early summer of 2021.

Naturally, there was considerable interest in the inter-relationships between SARS-CoV-2 viral infection or vaccination and rheumatic diseases and the impact of anti-rheumatic drugs on vaccination. The key findings are summarised in this report, including the impact of Rheumatology drugs including rituximab and JAK inhibitors in blunting humoral immune responses, which is not unexpected. Further work is needed on the impact of DMARDs on cell-mediated immunity to SARS-CoV-2 infection. Rheumatology cases fared well following vaccination, with little evidence for severe disease exacerbations beyond occasional case reports that are well recognised after infection or vaccination in general. On the flipside, the evidence for the use of anti-rheumatic drugs as therapy for severe COVID-19 pneumonia including tocilizumab and corticosteroids for severe COVID-19 has continued to accumulate.

Other highlights from the meeting included consolidation of the IL-23 blockers in psoriatic arthritis and further evidence for excellent safety. Unlike inflammatory arthritis, investigators embarking on exploratory studies into SLE-related nephritis have further work to do to etch out a niche for anti-IFN therapy. In the case of osteoarthritis, the use of molecular therapies aimed at cartilage regeneration or for the targeting of inflammation have not either worked or are a long way from the clinic.

We look forward to hopefully meeting again in person at EULAR 2022. For this to happen, the rheumatologist's natural enemy, the fully primed or auto-aggressive immune system that is responsible for so much of our workload, will hopefully show why it is also our greatest friend by warding off and intercepting SARS-CoV-2 mutants that could overcome the original vaccinations strategies and also progressively establish herd immunity. Let's hope so!

Sincerely,

Prof. Dennis McGonagle

Biography

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

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

COVID-19 Update

Rituximab or JAK inhibitors increase the risk of severe COVID-19

The risk of severe COVID-19 outcomes in patients with rheumatoid arthritis (RA) is 4 times higher for those using rituximab and 2 times higher for those using a JAK inhibitor compared with patients who use TNF inhibitors. For abatacept and IL-6-inhibiting DMARDs, this association was not found. This was the conclusion of a large study comparing COVID-19 severity in RA patients treated with different classes of DMARDs. These results demonstrated the importance of risk-mitigation strategies in RA patients on rituximab or JAK inhibitors [1].

To examine the effect of baseline use of different DMARD classes on COVID-19 severity in RA, 2,869 patients with resolved COVID-19 were selected from the COVID-19 Global Rheumatology Alliance physician registry. Treatment with rituximab (n=224), JAK inhibitors (n=306), abatacept (n=154), or IL-6 inhibitors (n=180) was compared with TNF inhibitors (reference group, n=809) on an ordinal COVID-19 severity scale (1: not hospitalised; 2: hospitalised without oxygen; 3: hospitalised with oxygen or ventilation; 4: death). Data was analysed via ordinal logistic regression analysis. Dr Jeffrey Sparks (Brigham and Women's Hospital, MA, USA) shared the results of this study.

Patients treated with rituximab or JAK inhibitors had a 4-fold or 2-fold increased risk of severe COVID-19 outcomes, respectively, compared with the reference group. In 85.4% of the cases, TNF inhibitor users were not hospitalised as a consequence of COVID-19. These percentages were significantly smaller in patients on rituximab (57.7%) or JAK inhibitors (72.6%). Baseline users of abatacept or IL-6 inhibitors were not hospitalised in 76.4% and 85.5% of the cases, respectively. In addition, treatment with rituximab or JAK inhibitors at COVID-19 onset resulted more often in hospitalisation with oxygen or ventilation (rituximab 22.0%; JAK inhibitors 15.3%; TNF inhibitors 7.4%) or death (rituximab 14.8%; JAK inhibitors 7.1%; TNF inhibitors 2.6%) than TNF inhibitor use. The primary multivariable analysis revealed that treatment with rituximab (OR 4.15; 95% CI 3.16–5.44) and JAK inhibitors (OR 2.06; 95% CI 1.60–2.65) was still associated with an increased risk of severe COVID-19 compared with TNF inhibitors after adjusting for covariates such as comorbidities, glucocorticoid use/dose, current disease activity, and concomitant use of hydroxychloroquine or conventional synthetic DMARDs. For treatment with abatacept (OR 1.26; 95% CI 0.88–1.80) and IL-6 inhibitors (OR 0.81; 95% CI 0.56–1.18) this increased risk was not demonstrated. The results were robust across sensitivity analyses.

Dr Sparks suggested that TNF inhibitors may have a potential protective effect on COVID-19 course of disease. This has been reported in a previous study among patients with rheumatic disease [2]. Nonetheless, the results of the current study should be interpreted with caution. Dr Sparks stressed the importance of COVID-19 risk management in RA patients on rituximab or JAK inhibitors, such as prioritising them for vaccination.

1. Sparks J, et al. Associations of Baseline Use of Biologic or Targeted Synthetic DMARDs with COVID-19 Severity in Rheumatoid Arthritis: Results from the COVID-19 Global Rheumatology Alliance Physician Registry. OP0006, EULAR 2021 Virtual Congress, 2–5 June.
2. Gianfrancesco M, et. al. Ann Rheum Dis. 2020;79(7):859-66.

Updates on COVID-19 vaccines in patients with rheumatic disease

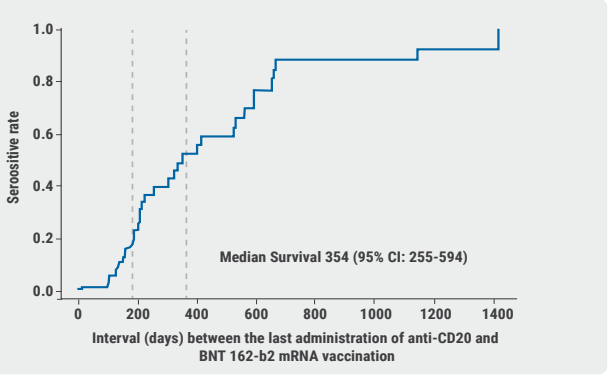
Rituximab is associated with severely impaired immunogenicity of the Pfizer BioNTech vaccine in autoimmune inflammatory rheumatic diseases (AIIRDs). Glucocorticoids, abatacept, mycophenolate mofetil, and methotrexate also undermine the immunogenicity of this vaccine in this population [1]. A second study demonstrated that COVID-19 vaccines are safe and well tolerated in patients with rheumatic and musculoskeletal diseases (RMD) [2].

Evidence on the efficacy and safety of mRNA vaccines in patients with AIIRDs is limited. In a prospective, observational, open-label, controlled multicentre study –presented by Dr Victoria Furer (Tel Aviv Sourasky Medical Center, Israel)– immunogenicity, safety, and efficacy of the Pfizer BioNTech vaccine were investigated in an adult AIIRD population (n=686, mean age 59 years) 2–6 weeks after the second vaccine dose was administered [1]. The vast majority (95.2%) were treated with immunosuppressants. The control group consisted of

121 healthy individuals 2–6 weeks after the second vaccine dose. A value of >15 binding antibody units (BAUs) was considered as a cut-off for seropositivity.

The seropositivity rate was 86% in the AIIRD group versus 100% in the control group. Patients treated with rituximab had the lowest seropositivity rates: 41.4% (OR 0.131; 95% CI 0.07–0.242; P<0.0001). The period between the most recent pre-vaccination administration of rituximab and time of vaccination had a significant effect on the immunogenicity of the vaccine. Seropositivity rate depended on the time of vaccination after the rituximab treatment and was 1.15% at 90 days, 18.39% at 180 days, and 52.18% at 365 days (see Figure).

Figure: The interval between the last administration of rituximab and time of vaccination is associated with seropositivity rate [1]



Other DMARDs that were associated with reduced seropositivity rates were glucocorticoids (66.2%), abatacept (62.5%), mycophenolate mofetil (64.3%), and to a lesser extent methotrexate (84.1%) (see Table). In addition, lower seropositivity rates were more often observed in patients >65 years (79.3%; OR 0.429; P=0.0027) and for certain AIIRD diagnoses: rheumatoid arthritis 82.1% (OR 0.305; P=0.01), idiopathic inflammatory myopathies 36.8% (OR 0.063; P=0.0002), and ANCA-associated vasculitis 30.8% (OR 0.043; P<0.0001).

Table: Seropositivity rates for different DMARDs [1]

DMARD	Seropositivity rate	OR	95% CI	P-value
Rituximab	41.4%	0.131	0.07–0.242	P<0.0001
Glucocorticoids	66.2%	0.476	0.262–0.866	P=0.015
Abatacept	62.5%	0.137	0.044–0.429	P=0.0007
Mycophenolate mofetil	64.3%	0.104	0.032–0.339	P=0.0013
Methotrexate	84.1%	0.577	0.311–1.072	P=0.082

Disease activity remained stable after vaccination for most AIIRD patients. One AIIRD patient died 2 weeks after vaccination, and 1 control subject had a mild SARS-CoV-2 infection and fully recovered. Mild AEs after vaccination were comparable in all patient groups. Some cases of herpes zoster (n=6), uveitis (n=2), herpes labialis (n=1), and pericarditis (n=1) were reported in the AIIRD population. Dr Furer argued that, to improve the immunogenicity of the Pfizer BioNTech vaccine, postponing treatment with rituximab or holding treatment with mycophenolate mofetil or abatacept should be considered.

A related study, presented by Dr Pedro Machado (University College London, UK) analysed safety data of COVID-19 vaccines (Pfizer BioNTech 78%, Moderna 5%, AstraZeneca 16%, other 1%) used in RMD patients (n=1,519; mean age 63; 68% women) from the COVAX registry [2]. The diagnostic groups consisted of inflammatory joint diseases (51%), connective tissue diseases (19%), vasculitis (16%), other immune-mediated inflammatory diseases (4%), and non-inflammatory RMDs (9%). All patients had received at least 1 dose of vaccine; 66% were fully vaccinated.

The results demonstrated that the safety profile of the vaccines among patients with RMD was similar to that of the general population. Following vaccination, disease flares were reported in 5% of the patients with inflammatory RMDs. AEs occurred in 31% of the patients. Pain at the injection site (19%), fatigue (11%), headache (7%), and generalised muscle pain (6%) were the most common AEs. Systemic or organ side effects were reported in 33 cases. These AEs were diverse and mostly mild or moderate. Severe AEs were reported in 2 cases: 1 case of transient hemiparesis in a patient with systemic sclerosis and systemic lupus erythematosus, and a case of giant cell arteritis in an elderly patient with osteoarthritis. Dr Machado concluded that the safety profiles of COVID-19 vaccines for RMD patients were reassuring.

1. Furer V, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD) compared to the general population: a multicenter study. LB0003, EULAR 2021 Virtual Congress, 2–5 June.
2. Machado PM, et al. COVID-19 vaccine safety in patients with rheumatic and musculoskeletal disease. LB0002, EULAR 2021 Virtual Congress, 2–5 June.

Immunomodulatory therapies for severe COVID-19: literature update

Efficacy and safety of immunomodulatory therapies used for the management of SARS-CoV-2 infection were analysed and summarised by means of a systematic literature review covering 401 papers, with the aim of informing the EULAR taskforce on COVID-19 immunomodulatory therapies and pathophysiology from a rheumatology perspective.

Adults with a proven SARS-CoV-2 infection, symptomatic or asymptomatic COVID-19, and without rheumatic disease prior to infection were included. Dr Alessia Alunno (University of Perugia, Italy) presented the results [1]. Glucocorticoid therapy in addition to standard of care (5 randomised clinical trials [RCTs]) showed a reduced mortality rate compared with standard treatment for oxygen-receiving (RR 0.89; 95% CI 0.79–1.00) and mechanically ventilated (RR 0.71; 95% CI 0.58–0.86) COVID-19 patients in the large RCT RECOVERY (NCT04381936; n=6,425). In contrast, the use of glucocorticoids in patients not receiving supplemental oxygen increased the mortality rate (RR 1.27; 95% CI 1.00–1.61). Older age of COVID-19 patients (>60 years) was associated with reduced mortality when they were treated with glucocorticoids (RR 0.75; 95% CI 0.56–1.01).

Five RCTs on tocilizumab did not demonstrate mortality benefits in COVID-19 patients. However, the largest included trial, REMAP-CAP (NCT02735707), did show a reduced mortality of additional tocilizumab treatment next to standard of care (RR 0.78; 95% CI 0.63–0.97). In addition, this trial showed that tocilizumab users had a lower risk of disease progression towards mechanical ventilation or death (RR 0.78, 95% CI 0.65–0.94). Clinical worsening or time to improvement were not influenced by tocilizumab administration.

Hydroxychloroquine did not provide mortality benefits for COVID-19 patients (5 RCTs). In fact, 1 RCT on hydroxychloroquine showed that administering this drug could increase mortality rate in this population (RR 1.18; 95% CI 0.90–1.56).

One anakinra RCT was included in the systematic review. No benefits were observed for this drug. The effect of baricitinib (1 RCT) on mortality rate in COVID-19 patients was not significant (RR 0.85; 95% CI 0.40–1.07). Dr Alunno added that, in oxygen-receiving patients, baricitinib plus remdesivir significantly improved mortality rate and shortened the time to recovery. Moreover, the rate of adverse events was not increased by the additional administration of baricitinib.

Dr Alunno concluded that robust evidence on the efficacy of immunomodulatory drugs for the treatment of SARS-CoV-2 infections is limited. The number of investigated outcomes is low and only a few drugs have been studied adequately.

Editor's note: Since the congress further data has emerged supporting the use of tocilizumab in severe COVID-19 as summarised in a recent meta-analysis [2].

1. Alunno A, et al. Immunomodulatory therapies for severe forms of COVID-19: a systematic literature review to inform EULAR points to consider. OP0287, EULAR 2021 Virtual Congress, 2–5 June.
2. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. JAMA 2021. DOI: 10.1001/jama.2021.11330.

New Developments in Rheumatoid Arthritis

JAK inhibitors and bDMARDs not associated with increased risk of serious infections in RA

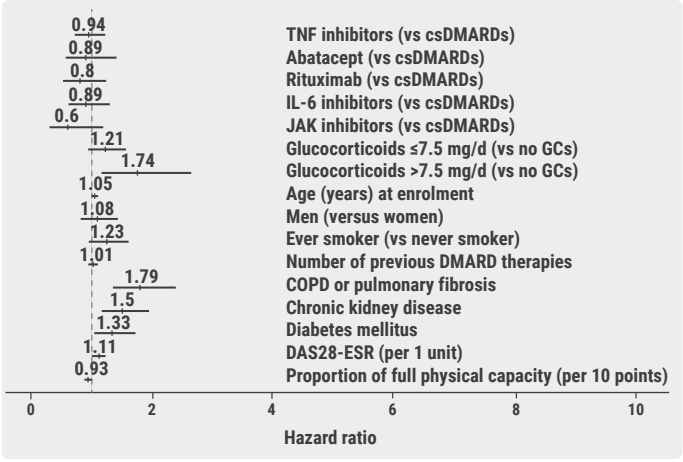
The risk of serious infections in elderly patients with rheumatoid arthritis (RA) was not increased in those who were treated with biologic (b)DMARDs or JAK inhibitors compared with patients treated with conventional systemic (cs)DMARDs. In contrast, certain comorbidities and a higher rate of disease activity were associated with a higher risk of serious infections in this population.

Mixed evidence exists on the risk of serious infections in elderly patients with RA treated with bDMARDs compared with csDMARDs. Moreover, the relation between JAK inhibitors and serious infections has not been investigated in elderly patients with RA. The current prospective cohort study collected data from the German RABBIT register to assess whether bDMARD and JAK inhibitor recipients are at an increased risk of serious infections compared with csDMARD-treated patients. Between 2007 and 2020, RA patients >70 years of age who had at least 1 follow-up appointment were included in the study. Dr Anja Strangfeld (German Rheumatism Research Centre Berlin, Germany) shared the results of the study.

In total, 2,274 elderly RA patients (mean age 76.0) were included and 616 serious infections in 425 patients were

reported. Crude rates of serious infections per 1,000 patient-years were 61.5 for csDMARDs, 72.8 for TNF inhibitors, 58.4 for abatacept, 73.8 for rituximab, 54.4 for IL-6 inhibitors, and 72.1 for JAK inhibitors. No significantly increased or reduced risks of serious infections were associated with bDMARD or JAK inhibitor use compared with csDMARD use (see Figure). Disease activity, represented by DAS28 erythrocyte sedimentation rate (HR 1.11), and physical capacity (HR 0.93) were significantly associated with the risk of serious infections. After stratifying for disease activity, glucocorticoid use was no longer significantly associated with an increased risk of serious infections. COPD (HR 1.79), chronic kidney disease (HR 1.50), and diabetes mellitus (HR 1.33) were also significantly associated with an increased risk of serious infections in this population of elderly RA patients. Overall, the data is very reassuring in relationship to the sleuth of new RA-targeting DMARDS in the last 20 years and infection risk in older subjects.

Figure: Hazard ratios for serious infections associated with rheumatic treatments [1]



1. Strangfeld A, et al. Elderly patients are not at increased risk of serious infections when receiving bDMARDs or JAK inhibitors compared to csDMARD treatment. OP0116, EULAR 2021 Virtual Congress, 2–5 June.

Remote management of RA is a feasible alternative for outpatient follow-up

Considering the limited access to healthcare facilities due to the current pandemic, remote patient management has become a topic of particular interest. Remote management of rheumatoid arthritis (RA) provides a feasible alternative for routine outpatient follow-up. This is the main conclusion of a prospective, longitudinal real-world study among RA patients in the UK [1].

Remote management of RA could lead to increasing patient confidence in self-care and increasing shared decision-making. Moreover, remote management reduces the burden on clinicians [2]. During the COVID-19 pandemic, remote management has become an important tool. Dr Mwidimi Ndosi (University of the West of England, UK) and colleagues investigated to what extent remote management and routine outpatient monitoring decisions are interchangeable.

The patients selected for this study (n=72; mean age 57.8; 87% women) continued usual care and clinical assessments, each month, every 3 months, or every 6 months, depending on disease activity. In addition, they performed a monthly self-assessment at home, including patient-reported outcome measures (PROMs) and the self-assessment questionnaires patient global assessment (PGA), Arthritis Self-Efficacy Scale (ASES), pain visual analogue scale, and fatigue visual analogue scale, as well as the self-reported components joint stiffness and flares. An independent health professional had access to the PROMs, questionnaires, and data considering medical history, ongoing therapy, and adverse events (AEs). Hospital-assessed clinical data was not provided (joint assessment, blood monitoring). Possible remote decisions were the addition or removal of a drug, to bring the patient in for review, or to not change therapy.

Remote decisions and usual outpatient follow-up decisions demonstrated fair agreement in the 57 decisions that could be matched. This result was observed for overall changes to RA therapy (kappa=0.24; P=0.07) and changes to biologic DMARD therapy (kappa=0.23; P=0.007). The self-assessment questionnaires identified 34 flares and 1 patient had to stop treatment due to an AE. This was recognised by remote and clinic-based evaluation. According to Dr Ndosi, the implementation of remote management could start in patients with low disease activity. Future studies should investigate if the addition of blood test monitoring adds value to remote decision-making.

1. Ndosi M, et al. Remote management of rheumatoid arthritis vs routine outpatient follow-up: a prospective, longitudinal real-world study. OP0155, EULAR 2021 Virtual Congress, 2–5 June.
2. Walker RC, et al. Int J Med Inform. 2019;124:78-85.

TOVERA: Ultrasound is a promising biomarker of early treatment response

In patients with very early rheumatoid arthritis (RA) on methotrexate plus tocilizumab combination therapy, ultrasound imaging was able to detect treatment response

in an earlier stage than clinical examination scores. Therefore, ultrasound is a potential imaging biomarker of treatment response in this specific patient population. These were findings of the open-label TOVERA study.

Ultrasound is an established imaging tool in RA management, though evidence on the applicability of ultrasound in very early RA patients on methotrexate plus tocilizumab combination therapy is limited. In the open-label, single-arm, phase 3 TOVERA study (NCT02837146), 44 very early RA patients naïve to DMARDs (mean age 46.7) completed the 24-week methotrexate (15–20 mg/week) plus tocilizumab (162 mg/week) induction therapy.

Both grayscale (GS) and Global OMERACT-EULAR Synovitis Score (GLOESS) scores detected a significant treatment response 2 weeks after treatment initiation on the 17-joint score (whole joint set; P<0.01), 12-joint score (P<0.05), and 10-joint score (wrists, MCP, ankles, MTP joints; P<0.05). In contrast, the clinical examination scores Disease Activity Score (DAS)-28 and Clinical Disease Activity Index (CDAI) only detected a significant treatment response at 4 weeks (DAS-28) or 8 weeks (CDAI; P<0.001) of therapy. Power-doppler scores recognised a first treatment response at 4 weeks. Patient-reported measures of disease activity –visual analogue scale (VAS) and Health Assessment Questionnaire (HAQ)– detected a first treatment response 8 weeks after the initiation of induction therapy (P<0.001). VAS fatigue scores only noticed treatment response after 12 weeks.

Dr Maria Stoenoiu (Cliniques Universitaires Saint-Luc, Belgium) argued that these results demonstrate that ultrasound is a promising imaging biomarker of early treatment response in very early RA patients. She concluded that this easy-to-use imaging tool could be used in addition to clinical examination instruments and adds value to the management and monitoring of very early RA patients. Certainly, such strategies may be useful for comparing the incremental benefit of DMARDs towards objective remission induction, but it is unclear whether it would alter long-term outcomes in clinical practice.

1. Stoenoiu MS, et al. Ultrasound as imaging biomarker of early response to tocilizumab and methotrexate in early rheumatoid arthritis – TOVERA, a longitudinal study. POS0259, EULAR 2021 Virtual Congress, 2–5 June.

The risks of polypharmacy in RA

Polypharmacy in rheumatoid arthritis (RA) is associated with high disease activity, an increased risk of serious adverse events (AEs), and a decreased treatment response. These were the main conclusions of a study among patients with RA using data from the French ESPOIR cohort. Moreover, the results indicated that polypharmacy is a potential measure for comorbidity [1].

Multimorbidity in RA is common and, as a consequence, 60% of RA patients are treated with multiple medications. Previous research has linked polypharmacy among RA patients to an increased risk of hospitalisation, increasing numbers of AEs, and a hampered treatment response [2-4]. This multicentre, prospective cohort study among French RA patients (n=543) primarily aimed to evaluate the association between polypharmacy and treatment response 1 year after the initiation of the first DMARD treatment, measured via Disease Activity Score (DAS)28-erythrocyte sedimentation rate (ESR) remission scores [1]. Secondary objectives were to assess treatment response at 5 and 10 years of follow-up, investigate the link between polypharmacy and AEs, and examine the association between polypharmacy and the comorbidity indices Rheumatic Disease Comorbidity Index (RDCI) and modified (m)RDCI. Polypharmacy included al specialty medication, except for other RA therapy, analgesics, NSAIDs, corticosteroids, and topical treatments.

The results demonstrated a trend towards a worse treatment response in the polypharmacy group (≥2 medications, 32.1% reaching DAS28-ESR remission) in comparison with the control group (0–1 medication, 67.9% reached remission; P=0.07). In the adjusted multivariate analysis, no association was found. The multivariate analysis showed a significant effect at 5 years (OR 0.60; 95% CI 0.38–0.94; P=0.03) and 10 years (OR 0.44; 95% CI 0.26–0.77; P=0.004) follow-up but only when comorbidity indices were not included. At 10 years follow-up, serious AEs (61/1,000 patient-years) occurred more often in the polypharmacy group (71.4%) than in the control group (57.8%; P=0.03). Finally, significant correlations were observed between polypharmacy and RDCI scores (r=0.47; P<0.01) and mRDCI scores (r=0.49; P<0.01), respectively. Dr Soraya Benamar (University Hospital of Montpellier, France) explained that these results are in accordance with recent trials investigating polypharmacy in RA. Furthermore, Dr Benamar suggested that polypharmacy is a potential easy-to-use measure of comorbidity. Future studies are needed to explore this option.

1. Benamar S, et al. Polypharmacy is associated with a poorer treatment response and increased risk of adverse events in early rheumatoid arthritis: Data from French cohort Espoir. OP0098, EULAR 2021 Virtual Congress, 2–5 June.
2. Filkova et al. J Rheumatol. 2017; 44(12):1786-93.
3. Ma et al. Ther Clin Risk Manag. 2019; 15:505-24.
4. Bechman et al. Rheumatology. 2019;58(10):1767-76.

ABBV-3373: A potential new therapeutic agent for RA

ABBV-3373 is a potential new drug for rheumatoid arthritis (RA) that has shown promising efficacy and safety results in a 24-week randomised, double-blind, double-dummy, proof-of-concept phase 2 trial [1]. This antibody-drug conjugate combines the working mechanisms of TNF inhibitor adalimumab and a glucocorticoid receptor modulator (GRM) to improve patient outcomes.

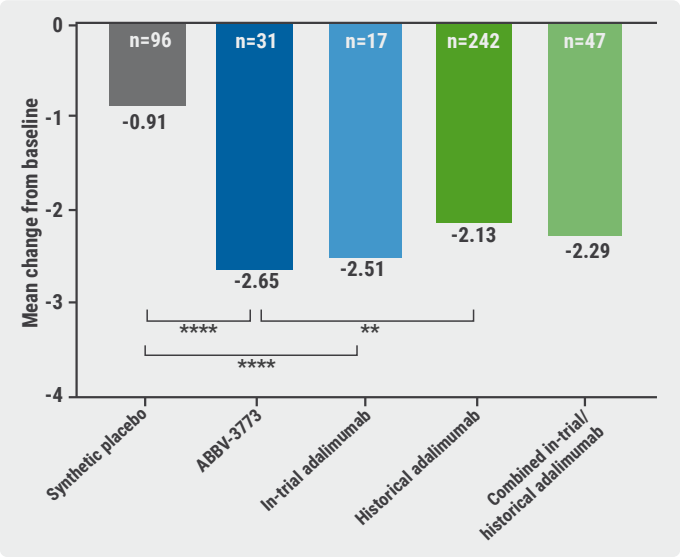
Glucocorticoids are highly effective in treating RA. However, the potential systemic side effects limit the long-term use of these drugs. ABBV-3373 is an antibody-drug conjugate consisting of adalimumab linked to a proprietary GRM, which is designed to use the favourable aspects of a TNF inhibitor and a glucocorticoid. GRMs can selectively induce a receptor conformation in a way that only activates a subset of downstream signalling pathways, thereby combining agonistic and antagonistic properties of glucocorticoids, depending on the tissue in which it is expressed. This targeted approach may potentially dampen systemic side effects [2].

In the current trial, RA patients were randomised 2:1 to placebo (n=96) or one of the experimental conditions: in-trial adalimumab (n=17; 80 mg subcutaneous every other week) or ABBV-3373 (n=31; 100 mg intravenous every other week). Efficacy and safety data of ABBV-3373 were compared with data of 242 historical adalimumab recipients, in-trial adalimumab users, and placebo users. Primary endpoint was the change from baseline 28-joint Disease Activity Score based on C-reactive protein (DAS28–CRP) scores at week 12.

The results were presented by Dr Frank Buttgereit (Charité University Medicine, Germany) and demonstrated patient benefits of ABBV-3373 over historical adalimumab users and placebo, represented as mean change on DAS28–CRP scores after 12 weeks of treatment: -2.65 for ABBV-3373 versus -2.13 for historical adalimumab (P<0.05) and versus -0.91 for placebo (P<0.001). No significant difference between DAS28–CRP mean changes of ABBV-3373 and in-trial adalimumab users was observed (see Figure).

Similar positive results were obtained for secondary outcome measures: DAS28 based on Erythrocyte Sedimentation Rate, Crohn's Disease Activity Index (CDAI), Simplified Disease Activity Index for RA (SDAI), ACR responses 20/50/70,

Figure: Change from baseline in DAS28–CRP at week 12 [1]



DAS28–CRP, 28-joint disease activity score based on C-reactive protein.
** P<0.05; **** P<0.001

and Health Assessment Questionnaire–Disability Index (HAQ–DI). Fewer AEs were reported in patients treated with ABBV-3373 (11, 35.5%) compared with in-trial adalimumab recipients (12, 70.6%). Nonetheless, 4 AEs in the ABBV-3373 population were considered serious: non-cardiac chest pain, pneumonia, upper respiratory tract infection, and anaphylactic shock (all n=1). Serious AEs were not reported in the in-trial adalimumab population. The safety profile of ABBV-3373 was fairly similar to that of adalimumab.

Dr Buttgereit argued that these findings demonstrate the potential of ABBV-3373 to provide benefits for RA patients compared with adalimumab. "All RA patients could benefit from the targeted delivery of this TNF inhibitor linked to a GRM".

1. Buttgereit F, et al. Efficacy and Safety of ABBV-3373, a Novel Anti-TNF Glucocorticoid Receptor Modulator Antibody Drug Conjugate, in Patients with Moderate to Severe Rheumatoid Arthritis Despite Methotrexate Therapy: A Phase 2a Proof of Concept Study. OP0115, EULAR 2021 Virtual Congress, 2–5 June.
2. Meijer OC, et al. Ann Endocrinol (Paris). 2018;79(3):107-11.

JAK inhibitors and bDMARDs show comparable effectiveness

JAK inhibitors show comparable effectiveness to biologic (b)DMARDs in rheumatoid arthritis (RA). That was the main conclusion of a comprehensive comparison between JAK inhibitors and bDMARD users in Swedish RA patients.

The oral administration and relatively low costs of JAK inhibitors are beneficial for RA patients. The first JAK inhibitors

approved by the EMA, tofacitinib and baricitinib, have not been thoroughly compared with other biologics prescribed for RA. Therefore, Mr Andrei Barbulescu (Karolinska Institutet, Sweden) performed a comprehensive comparative analysis of JAK inhibitors and biological DMARDs. For the analysis, he used Swedish national data on RA clinical measurements from different registries. Mr Barbulescu compared patient characteristics, retention rates, and clinical responses of patients treated with JAK inhibitors or bDMARDs.

Patients on JAK inhibitors (n=905, mean age 60) started their treatment later in the disease than non-TNF inhibitor recipients (n=1,920) and patients treated with TNF inhibitors (n=3,497). The median RA duration in years at treatment initiation was 13 for JAK inhibitors and abatacept, 10 for IL-6 inhibitors, 12 for rituximab, and 9 for TNF inhibitors. At treatment initiation, the 28-joint disease activity score (DAS28) was generally lower in those treated with JAK inhibitors (4.6) and non-TNF inhibitors (abatacept 4.8; IL-6 inhibitors 4.9; rituximab 4.7) compared with those treated with TNF inhibitors (4.4). Combination therapy of JAK inhibitors and methotrexate was observed in 40% of the JAK inhibitor users. This is less frequent than in most bDMARD recipients, including methotrexate co-treatment with abatacept (49.8%), rituximab (52.8%), and TNF inhibitors (61.6%), but similar to co-treatment with IL-6 inhibitors (39.7%).

After adjustment for demographics, disease activity, previous use of targeted synthetic DMARDS or bDMARDs, disease history, and co-medication with glucocorticoids or methotrexate, no significant differences were found in treatment retention or treatment response at 12 months. However, IL-6 inhibitors trended towards a better treatment response on several outcome measures compared with JAK inhibitors. These included a good EULAR response (defined as DAS28 ≤3.2 plus a decrease of >1.2), in which an 8.7% difference was observed for IL-6 inhibitors versus JAK inhibitors (95% CI -1.5 to 18.9), and DAS28–ESR <2.6, in which IL-6 inhibitors differed 5.9% from JAK inhibitors (95% CI -5.9 to 17.18).

In addition, JAK inhibitors performed slightly better than TNF inhibitors on all treatment response outcomes, which were CDAI remission, joint counts remission, HAQ improvement, DAS28–ESR remission, and good EULAR response. In conclusion, bDMARDs and JAK inhibitors showed comparable effectiveness in this study.

1. Barbulescu A. Comparative effectiveness of JAKi versus bDMARD; a nationwide study in RA. OP0122, EULAR 2021 Virtual Congress, 2–5 June.

Spondyloarthritis: Progression in Therapies

SELECT-AXIS: 64-week results of upadacitinib in active ankylosing spondylitis

Upadacitinib demonstrated lasting efficacy and no new safety issues in patients with active ankylosing spondylitis (AS). The 64-week results of the open-label extension phase of the SELECT-AXIS 1 phase 2/3 trial showed that this JAK inhibitor could help to address an unmet need in active AS patients [1].

The SELECT-AXIS 1 trial (NCT03178487) included 187 adult patients with active AS (defined as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 and back pain ≥4 on a numeric rating scale), who were naïve to biologic (b)DMARDs and had an inadequate response to NSAIDs at baseline. Patients were randomised to placebo (n=94, mean age 43.7) or 15 mg oral, once daily upadacitinib (n=93, mean age 47.0). Previously presented primary results demonstrated that upadacitinib was efficacious and well tolerated at 14 weeks of treatment [2].

The trial continued with a 90-week open-label extension period that enrolled 178 patients from the randomisation period. The current interim analysis reported efficacy and safety data of upadacitinib through 64 weeks and was presented by Dr Atul Deodhar (Oregon Health & Science University, OR, USA). A non-responder imputation (NRI) approach was used for the analysis.

The results showed that 72% of the patients who continued upadacitinib after the randomisation period achieved an Assessment in SpondyloArthritis International Society 40% (ASAS40) at week 64 (see Figure). In comparison, primary results after 14 weeks in SELECT-AXIS 1 demonstrated that 51.6% of participants had reached ASAS40 versus 25.5% of the placebo group. From the patients switching from placebo to upadacitinib in the open-label extension period, 70% reached ASAS40 after 64 weeks.

Secondary efficacy outcome measures demonstrated efficacy of upadacitinib as well in this interim analysis. This was measured by the BASDAI 50% response, which was 67% for those switching from placebo at week 14 versus 70% for those continuing on upadacitinib. Furthermore, Patient Global Assessment (PGA) change from baseline was -4.41 (switching from placebo) versus -4.44 (continued upadacitinib), and the Bath Ankylosing Spondylitis Functional Index (BASFI) change from baseline was -3.39 versus -3.53, respectively.

No new safety issues emerged from this analysis. Adverse events were reported 618 times; 14 were considered serious. No cases of serious infection, active tuberculosis, venous thromboembolic events, major cardiovascular events, gastrointestinal perforation, inflammatory bowel disease, renal dysfunction, or death were reported following upadacitinib treatment. Creatine phosphokinase elevation occurred in 28 cases. However, these cases were mostly asymptomatic and transient. None of the cases led to discontinuation of the study. Herpes zoster was diagnosed in 5 patients. Dr Deodhar argued that herpes zoster infections are a recurring problem in JAK inhibitor recipients. Therefore, vaccination against this virus in advance of upadacitinib treatment should be considered. This could especially be beneficial for older patients, who are at higher risk of a herpes zoster infection.

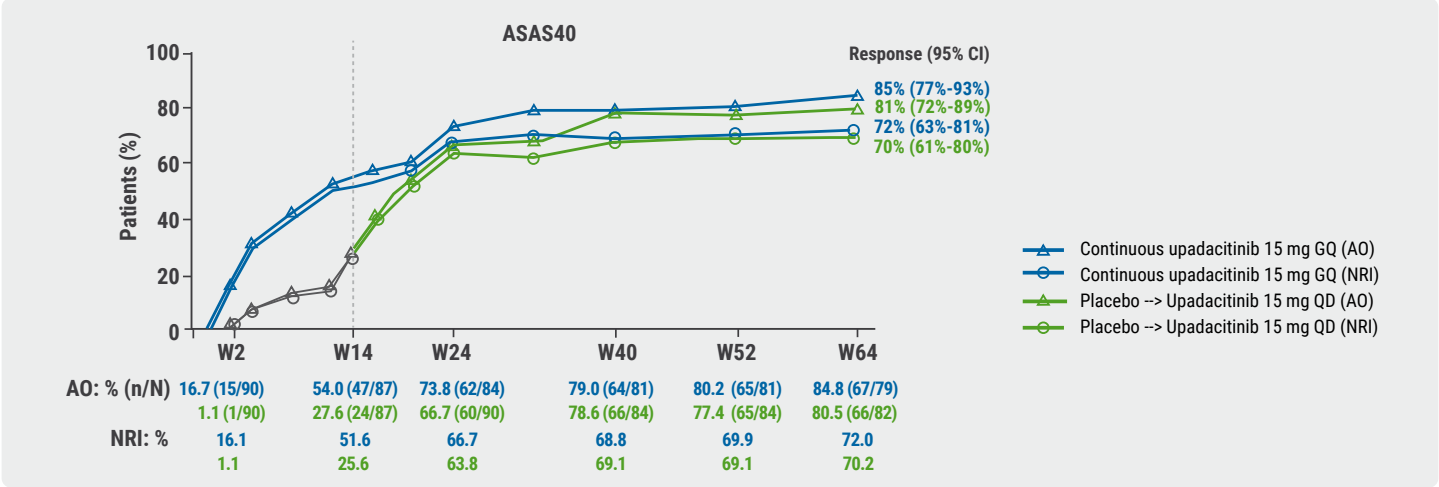
1. Deodhar A, et al. Efficacy and Safety of Upadacitinib in Patients with Active Ankylosing Spondylitis: 1-Year Results from a Randomized, Double-blind Placebo-controlled Study With Open-label Extension. OP0144, EULAR 2021 Virtual Congress, 2–5 June.
2. Van der Heijde D, et al. Lancet. 2019;394(10214):2108-17.

Guselkumab efficacious in PsA patients with inadequate response to TNF inhibition

Guselkumab was more efficacious than placebo in patients with psoriatic arthritis (PsA) who had an inadequate response or showed intolerance to 1 or 2 TNF inhibitors. Furthermore, the observed safety profile of guselkumab was reassuring [1]. The phase 3, double-blind, randomised, placebo-controlled COSMOS trial is the first study to assess an IL-23 inhibitor specifically in patients with PsA who failed prior TNF inhibitor treatment.

Guselkumab is a selective, monoclonal antibody targeting the IL-23p19 subunit. It has previously shown to be effective in patients with PsA in the phase 3 DISCOVER-1 and -2 trials [2,3]. In the COSMOS trial (NCT03796858), patients with active PsA who had failed TNF inhibitor treatment were randomised 2:1 to guselkumab (n=189) or placebo (n=96). Patients in the treatment arm received subcutaneous doses of 100 mg guselkumab at week 0 and week 4, and subsequently every 8 weeks. The primary efficacy endpoint was American College of Rheumatology (ACR)20 response at week 24. Dr Laura Coates (University of Oxford, UK) presented the findings of the study.

Figure: Efficacy of upadacitinib versus placebo over 1 year as measured by ASAS40 [1]



ASAS40, Assessment in SpondyloArthritis International Society 40%; AO, as observed; NRI, non-responder imputation; QD, once daily.

Baseline characteristics between the groups were similar. An ACR20 response was achieved in 44.4% of the patients in the guselkumab arm and in 19.8% of patients in the placebo arm (P<0.001). Subgroup analyses demonstrated that the efficacy of guselkumab was consistent across patients who had failed prior TNF inhibitor treatment due to a lack of efficacy and patients who had shown intolerance to TNF inhibitor treatment.

Adverse events were reported in 37% of the patients in the guselkumab arm and in 48% of the patients who received placebo. Serious adverse events were observed in 3% of the patients in both arms of the trial. No new safety issues were reported.

1. Coates LC, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis who demonstrated inadequate response to tumor necrosis factor inhibition: week 24 results of a phase 3b randomized, controlled study. OP0230, EULAR 2021 Virtual Congress, 2–5 June.
2. Deodhar A, et al. Lancet 2020;395(10230): 1115–25.
3. Mease PJ, et al. Lancet 2020;395: 1126–36.

Faecal microbiota transplantation not effective in active peripheral PsA

Faecal microbiota transplantation (FMT) as an add-on therapy to methotrexate was inferior in the treatment of active peripheral psoriatic arthritis (PsA) in the proof-of-concept, randomised, sham-controlled FLORA trial [1].

The exploratory FLORA study (NCT03058900) investigated the safety and efficacy of a single-donor FMT in 31 adult patients with active peripheral PsA (≥3 swollen joints). In addition to methotrexate treatment, participants were randomised to FMT (n=15, mean age 48.9) or sham transplantation (n=16, mean age 52.4). Primary endpoint was the proportion of patients with treatment failure (i.e., needing treatment intensification) at 26 weeks of therapy, based on shared decision-making between patient and physician. Safety was assessed by comparing the number of treatment-induced serious adverse events (AEs).

The results demonstrated that treatment failure at 26 weeks of therapy had occurred more often in the FMT group (60%) than in the sham group (19%; HR 4.87; 95% CI 1.31–18.18; P=0.018). Components of treatment failure included patients starting biologic DMARD treatment (FMT 53% vs sham 19%), receiving intra-articular glucocorticoid injection(s) (FMT 13% vs sham 6%), or starting non-methotrexate conventional synthetic DMARD therapy (FMT 0% vs sham 6%). Compared with baseline, Health Assessment Questionnaire Disability Index (HAQ-DI) scores, a key secondary efficacy endpoint, had decreased significantly more in the sham group (-0.30) than in the FMT group (-0.07) (difference between groups 0.23; 95% CI 0.02–0.44; P=0.031). A similar difference was observed for the SPARCC Enthesitis Index score (FMT -1.9 vs sham -4.3). American College of Rheumatology (ACR)20 response was reached in 47% (FMT) and 50% (placebo). The number of AEs was similar across groups (FMT 57 vs placebo 53). Infections were reported in 9 patients (FMT 3 vs placebo 6). The infections that occurred in the FMT group were pneumonia, cystitis, and diverticulitis. No serious AEs were detected with FMT therapy in the safety analysis.

Although FMT was inferior to sham in this trial, Dr Maja Skov Kragsnaes (University of Southern Denmark, Denmark) argued that other trials should investigate the efficacy and safety of FMT. "The most important finding of this study is the feasibility of FMT. There are no preliminary safety issues and patients reacted positively to the application of this therapy. We have to learn more about the immunological effects of FMT and thoroughly analyse the composition of microbiota in donors and recipients to find the right donor for each patient."

1. Skov Kragsnaes M, et al. Safety and efficacy of faecal microbiota transplantation for active peripheral psoriatic arthritis: an exploratory randomised placebo-controlled trial. OP0010, EULAR 2021 Virtual Congress, 2–5 June.

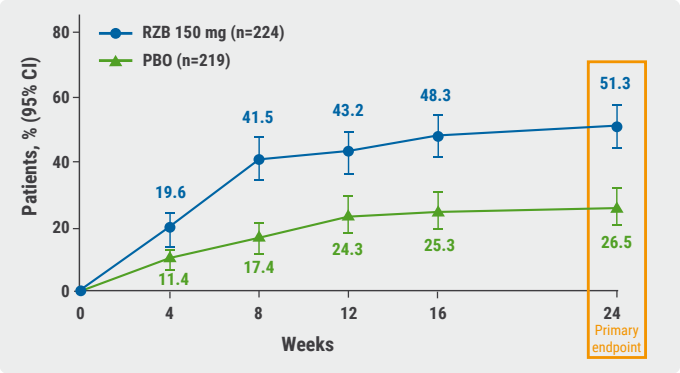
Risankizumab meets primary and ranked secondary endpoints in PsA

Treatment with risankizumab led to significantly greater improvements in signs and symptoms than placebo in patients with active psoriatic arthritis (PsA) who have shown inadequate response or intolerance to 1 or 2 biologic therapies or ≥1 DMARD therapy. In addition, no specific safety issues were observed at 24 weeks in the phase 3 randomised, double-blind KEEPsAKE 2 trial [1].

Risankizumab is a humanised, monoclonal antibody targeting IL-23. This interleukin has been implicated in the pathogenesis of PsA [2]. Currently, risankizumab is approved for the treatment of moderate-to-severe plaque psoriasis in adults. In the KEEPsAKE 2 trial (NCT03671148), adult patients with active PsA (≥5 tender joints and ≥5 swollen joints) and an inadequate response to biologics or conventional synthetic DMARDs (n=444) were randomised to risankizumab (n=224, mean age 53) or placebo (n=219, mean age 52). Risankizumab 150 mg was administrated at week 0 and 4, followed by once every 12 weeks. A double-blind period of 24 weeks is followed by an open-label extension period. Prof. Andrew Östör (Monash University, Australia) presented the week 24 results. The primary endpoint was a ≥20% improvement on the American College of Rheumatology (ACR)20 response at week 24.

The primary endpoint was met (see Figure). Significantly more patients in the risankizumab arm (53%) had an improvement in ACR20 score than patients in the placebo arm (26.5%; P<0.001).

Figure: The ACR20 response for treatment with risankizumab versus placebo [1]



*P≤0.05; ***P≤0.001 versus placebo.

Furthermore, all ranked secondary endpoints were met: change in Health Assessment Questionnaire Disability Index (HAQ-DI; risankizumab -0.22 vs placebo -0.05; P<0.001); Psoriasis Area and Severity Index 90 (PASI 90; risankizumab 55.0% vs placebo 10.2%; P<0.001), ACR20 at week 16 (risankizumab 48.3% vs placebo 25.3%; P<0.001), minimal disease activity (risankizumab 25.6% vs placebo 11.4%; P<0.001), change in SF-36 PCS (risankizumab 5.9 vs placebo 2.0; P<0.001), and change in FACIT-Fatigue (risankizumab 4.9 vs placebo 2.6; P<0.01). Non-ranked secondary efficacy endpoints demonstrated patient benefits of risankizumab as well. These included ACR50 response (risankizumab 26.3% vs placebo 9.3%; P<0.001), ACR70 response (risankizumab 12.0% vs placebo 5.9%; P<0.05), resolution of enthesitis (risankizumab 42.9% vs placebo 30.4%; P<0.01), and resolution of dactylitis (risankizumab 72.5% vs 42.1%; P<0.001).

Treatment-emergent adverse events (AEs) occurred in 55.4% (risankizumab) and 54.8% (placebo) of patients. Respectively, 4.0% (risankizumab) and 5.5% (placebo) of the treatment-emergent AEs were considered serious. Active tuberculosis or other opportunistic infections were not observed in either treatment group. No anaphylactic reactions were reported. Other than upper respiratory tract infections, no treatment-emergent AE was observed in ≥5% of the patients in either arm of the study. Prof. Östör concluded that risankizumab was well tolerated for active PsA and that the safety profile was similar to that of risankizumab treatment in moderate-to-severe psoriasis.

1. Östör A, et al. Efficacy and Safety of Risankizumab for Active Psoriatic Arthritis, Including Patients With Inadequate Response or Intolerance to Biologic Therapies: 24-Week Results From the Phase 3, Randomized, Double-blind, KEEPsAKE 2 Trial. OP0228, EULAR 2021 Virtual Congress, 2–5 June.
2. Boutet M-A, et al. Int J Mol Sci. 2018;19(2):530.

Prognostic factors for minimal disease activity in early psoriatic arthritis revealed

Minimal disease activity (MDA) following a treat-to-target (T2T) strategy in early psoriatic arthritis (PsA) can be predicted by a combination of factors, including Tender Joint Count (TJC)68, patient global assessment (PGA) of disease activity, pain, and the absence of enthesitis and dactylitis. As a consequence, these prognostic factors could be useful in predicting therapy outcomes and managing patient expectations in early PsA patients.

Prof. Tatiana Korotaeva (Nasonova Research Institute of Rheumatology, Russia) emphasised that this is the first study to investigate prognostic factors for MDA in early PsA following a T2T strategy. Early PsA patients (n=77, mean age 36.9) were given methotrexate therapy for 12 months. Biologic DMARDs were added for 29 patients between 3 and 9 months due to therapy ineffectiveness. At baseline and after 12 months of therapy, disease activity and the disease characteristics of PsA and psoriasis duration were evaluated. Logistic regression analysis was conducted to compare patients who had achieved MDA (n=45) and not achieved MDA (n=32) at 12 months.

The results showed a significant association between achieving MDA at 12 months and baseline for TJC68 (<3; P<0.001), Swollen Joint Count (SJC)66 (<3; P<0.001), pain visual analogue scale (≤15 mm; P<0.001), Patient Global Assessment (PGA) of disease activity (≤20 mm; P<0.001), C-reactive protein (≤5 mg/L; P=0.03), absence of dactylitis (P=0.029), absence of enthesitis (Leeds Enthesitis Index [LEI] and plantar fascia; P=0.003), Health Assessment Questionnaire (HAQ; ≤0.5; P=0.001), absence of nail damage (P=0.012), and fatigue (FACIT>30, P=0.021). In combination, these features were predictive of reaching MDA in early PsA patients (OR 9.68; 95% CI 4.6–20.4). Prof. Korotaeva stressed that these results could have clinical value: "The prognostic factors revealed in this study should be taken into account when assessing an early PsA patient, because it helps us predict treatment outcomes in clinical practice."

1. Loginova EY, et al. Prognostic factors associated with achieving minimal disease activity in early psoriatic arthritis patients treated according to treat to target strategy. POS0192, EULAR 2021 Virtual Congress, 2–5 June.

Imaging in Large-Vessel Vasculitis

PET/CT is a reliable measure of disease activity in LVV, but does not predict future relapses

PET/CT showed a discriminating value in measuring disease activity in large-vessel vasculitis (LVV). This finding was consistent in giant cell arteritis (GCA) and Takayasu's arteritis (TAK) subgroups. Therefore, PET/CT could be a reliable tool in the assessment of disease activity in LVV. Surprisingly, higher PET Vascular Activity Score (PETVAS) scores during clinical remission were not predictive of future relapses [1].

Disease activity assessment in LVV lacks validated biomarker-based scoring systems. PET/CT might be the imaging biomarker that is needed, as it has shown promising results in recent studies [2]. The current study assessed whether PETVAS can discriminate between clinically active and inactive LVV (both GCA and TAK) in a single-centre cohort study. Patients with radiographic evidence of LVV (n=100) were followed from 2007 until 2020 and received complete assessments (clinical, laboratory, imaging) at baseline, annually, and when relapse was suspected. PETVAS was calculated for each PET/CT scan and compared with the clinical examination of disease activity status.

Dr Elena Galli (University of Modena and Reggio Emilia, Italy) presented the results. During the study, 474 PET scans were performed. Logistic regression analysis demonstrated that higher mean PETVAS scores were associated with clinically active LVV (10.6) versus inactive LVV (4.4; OR 1.15; P<0.0001). The correct subdivision of active and inactive LVV patients was further confirmed by the following parameters (all P<0.001): mean prednisone dose (active 29.3 vs inactive 6.9 mg/day), mean erythrocyte sedimentation rates (active 55.5 vs inactive 20.3 mm/hour), mean C-reactive protein rates (active 5.5 vs inactive 0.7 mg/dL), and percentage of patients with ≥1 clinical symptom suggestive of active LVV (active 78.5% vs inactive 4%).

The discriminative value of PETVAS was consistent in the GCA (OR 1.12; P<0.0001) and TAK (OR 1.22; P<0.0001) subgroups. The computed ROC curves demonstrated acceptable predictive values of PETVAS scores differentiating between clinically active and inactive patients in the total population (AUC 0.73) and in the GCA (AUC 0.70) and TAK (AUC 0.79) subgroups. Nevertheless, higher PETVAS scores during low clinical disease activity (255 observations in 81 patients, 34 detected relapses) were not associated with a higher risk of clinical relapse (HR 1.04; P=0.25). According to Dr Galli, this finding is not well understood and needs to be unravelled in future research. Such subclinical vascular changes certainly need careful consideration on the timing and implications of PET scanning in GCA.

1. Galli E, et al. The role of positron emission tomography/computed tomography (PET/CT) in disease activity assessment in patients with large vessel vasculitis. OP0069, EULAR 2021 Virtual Congress, 2–5 June.
2. Grayson PC, et al. Arthritis Rheumatol. 2018;70(3):439-49.

Ultrasound is useful for disease monitoring in giant cell arteritis

Disease activity in giant cell arteritis (GCA) patients can be well monitored by ultrasound. The number of temporal arterial segments with halo sign, and temporal arterial intimal-media thickness were sensitive to change over 24 weeks. Moreover, halo features and disease activity markers demonstrated significant associations. These results were not found for axillary arterial halo features [1].

In patients aged ≥50 years, GCA is the most prevalent form of primary vasculitis. Irreversible blindness occurs in up to 30% of the cases. Although high dose glucocorticoids are an effective treatment, toxicity is a major problem and occurs in over 80% of patients. Therefore, a correct diagnosis and accurate monitoring of the disease are important. In prior studies, a non-compressible halo sign of the temporal and axillary arteries has demonstrated discriminative value for diagnosing GCA [2].

The current 2-centre, prospective study aimed to assess the potential of ultrasound for monitoring newly diagnosed GCA patients by analysing the sensitivity to change of ultrasound halo characteristics, and their connection to disease activity and glucocorticoid therapy. To this end, ultrasound features of patients with clinical relapse were assessed. A total of 49 patients with ultrasound-confirmed GCA (mean age 78.2, 73.5% women) were included in the study. The sensitivity of halo to change was calculated by the mean difference of halo

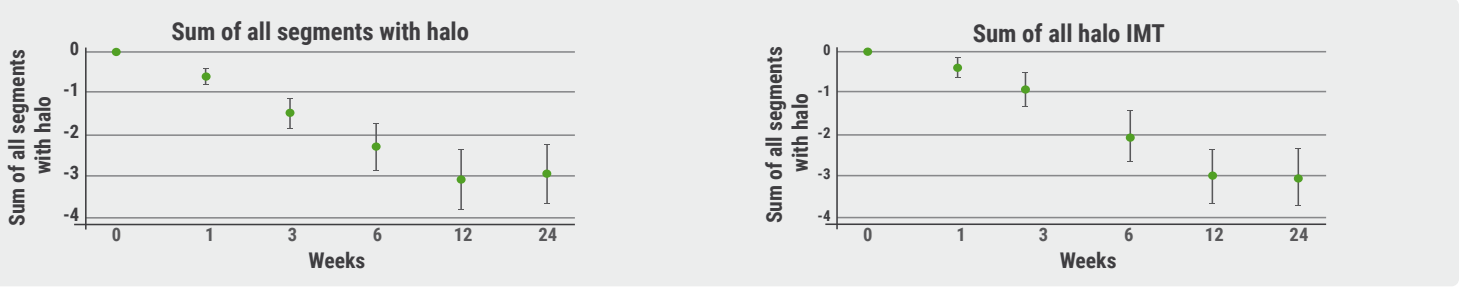
features (non-standardised variation) between baseline and the different timepoints (1, 3, 6, 12, and 24 weeks). Dr Cristina Ponte (Hospital de Santa Maria Lisbon, Portugal) shared the results of the study.

The sum of all arterial segments with halo –temporal and axillary arteries combined– demonstrated halo sensitivity to change over 24 weeks at all timepoints compared with baseline. The sum of halo intima-media thickness (IMT) demonstrated sensitivity to change at these timepoints as well. When temporal and axillary arteries were evaluated separately, only the sum of temporal arterial segments with halo and accessory IMT were sensitive to change at all timepoints (see Figure).

A significant association was found between the sum of all segments with halo and disease activity as measured by erythrocyte sedimentation rates, C-reactive protein, and Birmingham Vasculitis Activity Score (all P<0.05). Corresponding correlations for the sum of axillary halo segments and ESR, CRP, and BVAS were not significant. Correlations were similar for the sum of IMT of the separate arteries. In addition, a significant correlation was found between glucocorticoid cumulative dose and the sum of temporal segments with halo (-0.34; P<0.05). The sum of all segments with halo was related to the probability of being in disease remission, defined as an absence of relapse plus prednisone dose <30 mg/day (OR 0.47). Halo sign features of temporal segments were also associated with the probability of being in disease remission (OR 0.39). Finally, the sum of all segments with halo (P=0.0012) and temporal segments with halo (P=0.0012) were predictive of relapse. Dr Ponte concluded that ultrasound is a valuable tool in the monitoring of GCA patients: "A composite score of halo size and extent could be used to assess disease activity and treatment response in GCA patients."

1. Ponte C, et al. Ultrasound halo sign as a potential monitoring tool for patients with giant cell arteritis: a prospective analysis. OP0055, EULAR 2021 Virtual Congress, 2–5 June.
2. Dejaco C, et al. Ann Rheum Dis 2018;77(5):636-643.

Figure: Halo sensitivity to change during disease follow-up [1]



IMT, intima-media thickness.

Prevention in Rheumatic Diseases

Air pollution predicts decreased response to biological treatment in rheumatic diseases

A poor response to biological (b)DMARDs in patients with rheumatic diseases (RMDs) is associated with environmental air pollution. This was the main result of a case-crossover study among Italian RMD patients, and it adds to the increasing evidence that air pollution is a relevant factor in rheumatic diseases.

For this study, data was collected from the registry of biological therapies of the University of Verona. Daily air pollution data (2013–2018) of the Verona area and data on RMD patients within this area were examined. The case-crossover analysis included the patients who had experienced a stable period of ≥6 months of bDMARD therapy with ≥1 low disease activity (LDA) visit plus a treatment switch or swap visit (flare visit) due to drug

inefficacy (n=280). Patients who switched or swapped bDMARDs due to adverse events or drug intolerance were excluded from further analysis. Air pollution concentrations of the 60-day periods prior to the LDA visit and the flare visit were compared.

The results demonstrated that the mean concentrations of air pollutants were significantly higher prior to the flare visit compared with the LDA visit (P<0.001). In addition, ROC curves demonstrated that the combination of LDA and air pollution was a better predictor for therapy switch or swap than LDA alone. Dr Giovanni Adami (University of Verona, Italy) emphasised that these results show a direct association between environmental air pollution and a poor response to bDMARDs in RMD patients. "The ROC curves show that air pollution is an independent predictor of response to bDMARDs. When considering 100 bDMARD therapy switches or swaps, approximately 5 of them can be ascribed to the sole effect of air pollution." This interesting work certainly needs replication in larger cohorts.

1. Adami G, et al. Air pollution is a predictor of poor response to biological therapies in chronic inflammatory arthritides. POS0644, EULAR 2021 Virtual Congress, 2–5 June.

Passive smoking associated with an increased risk of RA

Exposure to passive smoking in childhood and/or adulthood is associated with an increased risk of rheumatoid arthritis (RA). This was found in the large prospective E3N-EPIC cohort study of French women. The effect is more pronounced in women who have also actively smoked during their lives. Furthermore, passive smoking during childhood could lead to an earlier onset of RA [1].

Active smoking is an established risk factor for RA [2]. The role of passive smoking in the development of RA has not been studied thoroughly. The E3N-EPIC cohort study focuses on diet and hormones as major components of women's health and the team performs analytical epidemiological research with interests in environment. The current analysis of E3N-EPIC was presented by Dr Yann Nguyen (Université Paris-Saclay, France) and aimed to fill this gap in the literature.

The study included 79,806 women (mean age at baseline 49.0); 698 incident RA cases have been identified since the initiation of the project in 1990. At baseline, participants were asked whether they were exposed to passive smoking in their childhood or adulthood. A cox proportional hazards model was used to analyse the data. The adjusted model controlled for active smoking, passive smoking exposure in childhood or adulthood, educational level, and baseline BMI. Data was stratified on active smoking status (ever-smoker or never-smoker).

Passive smoking in childhood (non-cases 13.5% vs RA cases 16.3%; HR 1.24; 95% CI 1.01–1.51) and adulthood (non-cases 53.6% vs RA 57.45%; HR 1.19; 95% CI 1.02–1.40) were significantly associated with an increased risk of RA. Among the participants exposed to passive smoking, the effect was larger for ever-smokers compared with never-smokers (absolute risk 53.67/100,000 vs 47.59/100,000 per year). Both these subgroups had an increased risk of RA compared with never-smokers with no exposure to passive smoking: being a never-smoker with exposure to passive smoking had an HR 1.33 (95% CI 1.08–1.6), ever-smoker plus exposure to passive smoking had an HR 1.50 (95% CI 1.22–1.84).

Participants who were not exposed to passive smoking and never smoked had a later age of disease onset (mean age 66.5) compared with participants who were exposed to passive smoking (mean age 63.7), had actively smoked (mean age 63.4), or had been exposed to passive smoking and had actively smoked (mean age 62.3). In addition, in the subgroup of the childhood passive smoking, ever-smokers had an earlier age of RA onset than never-smokers (mean age 60.6 vs 64.2). Dr Nguyen summarised the findings by saying that exposure to passive smoking in childhood and/or adulthood is associated with an increased risk of RA, and that passive smoking in childhood could lead to an earlier age of RA onset. He suggested that the results could be explained by a citrullination effect of passive smoking in genetically predisposed individuals.

1. Nguyen Y, et al. Association between passive smoking in childhood and adulthood and rheumatoid arthritis: results from the French E3N-EPIC cohort study. OP0010, EULAR 2021 Virtual Congress, 2–5 June.
2. Di Giuseppe D, et al. Arthritis Res Ther. 2014;16(2):R61.

Gene-Environment Interaction in Gout

Gene-diet and gene-weight interactions associated with the risk of gout

Adhering to the healthy Dietary Approaches to Stop Hypertension (DASH) diet decreased the risk of gout in women. This effect was more pronounced in genetically predisposed individuals. Also, a large proportion of incident gout cases can be accounted to excess weight in addition to genetic predisposition. These were the main conclusions of 2 prospective cohort studies investigating gene-environment interaction effects in gout [1-2]. The authors concluded that public interventions targeting diet and excess weight could have a big impact on the growing number of incident gout cases worldwide.

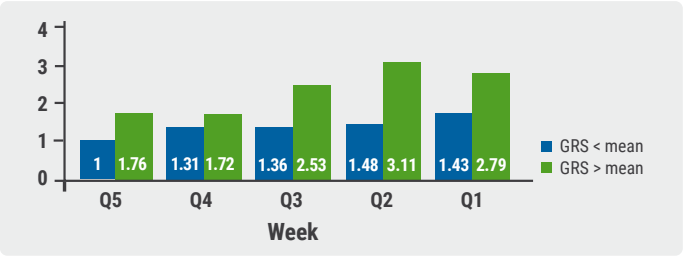
Although gout predominantly occurs in men, a Global Burden of Disease Study analysis revealed a rise in gout burden worldwide, especially among women [3]. Therefore, studying this condition in women has become increasingly important.

Dr Chio Yokose (Massachusetts General Hospital, USA) presented the results of 2 separate analyses from 2 prospective general health cohort studies: Nurses' Health Study (NHS; n=18,247 women; 1984–2018) and the Health Professionals Follow-Up Study (HPFS; n=10,899 men; 1986–2018).

In the NHS, 530 incident gout cases were discovered; 983 cases were observed in the HPFS. Genetic risk scores (GRS) were calculated based on 114 urate SNPs from European ancestry meta-analyses. Biennial health questionnaires including incident gout, BMI, and data on exposure to the DASH diet (considered healthy) and western diet (considered unhealthy) were collected. The first analysis assessed the potential interaction effect between genetic predisposition and diet on incident gout in US women, based on data from the NHS [1]. Cox proportional hazards model was used to analyse the association between genetics, diet, and the risk of incident gout. Based on GRS scores, participants were divided into 2 groups: those with an elevated genetic risk of gout (GRS above the mean) and those with a low genetic risk of gout (GRS below the mean). Diet adherence was categorised in quintiles. Three BMI groups were computed: normal weight (BMI <25), overweight (BMI 25–29.9), and obese (BMI ≥30). The model was adjusted for known risk factors of gout, such as age, BMI, red meat consumption, and the use of diuretics.

The risk of gout increased in women who adhered less to the DASH diet, especially in genetically predisposed women. The relative risk of women with high GRS increased from 1.76 (best adherence to DASH diet) to 2.79 (worst adherence to DASH diet; see Figure). In women with low GRS, the relative risk increased from 1 (best adherence to DASH diet) to 1.43 (worst adherence to DASH diet). Subsequent interaction analysis trended towards significance, with a relative excess risk due to interaction (RERI) of 0.57 (P=0.06). No genetics-diet interaction effect on incident gout was observed for the western diet (RERI 0.20; P=0.52).

Figure: Joint impact of DASH diet and GRS on the relative risk of incident gout in women [1]



GRS, genetic risk score; DASH, Dietary Approaches to Stop Hypertension; Q, quintile of diet adherence: Q1 is lowest adherence, Q5 is highest adherence.

The second analysis was based on both cohorts and examined to what extent excess weight and genetic predisposition for gout interact on the risk of incident gout. Although excess weight is an established risk factor for gout, weight-gene interaction effects have not yet been analysed in prior gout studies.

Results demonstrated that excessive weight in men was related to an increased risk of incident gout. Analysis of the GRS showed that this effect was amplified in genetically predisposed men. Relative excess risk for excess weight (overweight or obese) compared with normal weight trended towards significance (P=0.08). The investigated interaction

effect was more profound among women with excess weight. Additive interaction analysis confirmed this; incident gout was higher in overweight and obese women with a high genetic risk compared with overweight and obese women with a low genetic risk (RERI 1.69; P<0.01).

Dr Yokose argued that the results of these 2 prospective cohort studies suggest that dietary interventions and lifestyle interventions targeting weight can significantly reduce the number of gout cases. Women who have a genetic predisposition for gout could particularly benefit from this. However, further work is needed before a GRS could be applied to gout prediction.

1. Yokose C, et al. Gene-Diet Interaction on the Risk of Incident Gout Among Women: Prospective Cohort Study over 34 Years. OP0203, EULAR 2021 Virtual Congress, 2–5 June.
2. Yokose C, et al. Does Excess Weight Affect Gout Risk Differently Among Genetically Predisposed Individuals? Sex-Specific Prospective Cohort Findings over > 32 Years. OP0202, EULAR 2021 Virtual Congress, 2–5 June.
3. Safiri S, et al. Arthritis Rheumatol. 2020; 72(11):1916-27.

What Is New in Systemic Lupus Erythematosus

Intensified treatment regimen of anifrolumab for lupus nephritis is promising

An intensified treatment regimen of anifrolumab showed superiority over placebo on several clinical endpoints for patients with active, proliferative lupus nephritis (LN) [1]. The results of the randomised, placebo-controlled, double-blind phase 2 TULIP-LN trial therefore encourage further efficacy and safety assessment of anifrolumab in this population.

Anifrolumab, a type 1 interferon (IFN) receptor-targeting antibody, has demonstrated benefits for patients with moderate-to-severe systemic lupus erythematosus (SLE) in prior phase 3 trials [2,3]. However, patients with active, proliferative LN were not included in these studies. Since up to 40% of patients with SLE develops LN, and LN could lead to glomerular and tubulointerstitial damage, further evaluation of the use of anifrolumab in this population is required. In addition, type 1 IFN signalling is involved in LN pathogenesis, providing another rationale for investigating anifrolumab in LN patients.

In the TULIP-LN phase 2 trial (NCT02547922), 147 patients with active proliferative LN were randomised 1:1:1 to anifrolumab basic regimen (300 mg intravenous every 4 weeks), anifrolumab intensified regimen (900 mg for 3 doses, 300 mg thereafter, intravenous every 4 weeks), or placebo (intravenous every 4 weeks) in addition to standard therapy. The primary endpoint was the difference in change from baseline in 24-hour urine protein-to-creatinine ratio (UPCR) for combined anifrolumab regimens versus placebo at week 52.

The primary endpoint was not met: geometric mean change from baseline in 24-hour UPCR between placebo and the 2 regimens was not significantly different (P=0.905). Individually, no differences were observed between the 24-hour UPCR geometric mean ratio of placebo versus the basic regimen (1.10; 95% CI 0.61–1.99; P=0.741) and versus the intensified regimen (0.96; 95% CI 0.55–1.69; P=0.895). Numerical improvements of this measure over placebo were observed for both anifrolumab regimens at week 12 and week 24, and at week 36 for the intensified regimen. Pharmacokinetics exposure and pharmacodynamics exposure showed suboptimal results for the basic regimen group. Therefore, the authors focussed on the intensified regimen group for the secondary outcome measures.

Patients in the intensified regimen showed no difference in attained complete renal response (CRR; +14.3%, P=0.162). Nonetheless, a significant difference was observed for CRR with inactive urine sediments (+27.6%, P=0.003). SLE Disease Activity Index (SLEDAI)-2K (-2.6 vs -1.3); Physician's Global Assessment (-0.98 vs -0.66), and Patient Global Assessment (-16.7 vs -8.7) showed numerical benefits of the anifrolumab intensified regimen versus placebo. Finally, lupus serological tests showed numerical benefits of anifrolumab treatment:

C3 improvements if C3 was low at baseline (median change -0.28 vs -0.14 g/L); and anti-dsDNA reductions (median change -73.2 vs -11.0 units/mL).

The safety profile was similar to that of non-renal SLE patients, which was provided in previous anifrolumab trials. Adverse events occurred in 93.8% of the anifrolumab-treated patients and in 89.8% of the placebo patients. There were respectively 10, 9, and 8 cases of serious adverse events in the basic regimen arm, intensified regimen arm, and the placebo arm. Herpes zoster occurred more often in anifrolumab recipients (16 cases) than in placebo patients (4 cases). Prof. David Jayne (University of Cambridge, UK) concluded that the results of this study support further investigation of the intensified regimen of anifrolumab in patients with active, proliferative LN.

1. Jayne D, et al. Randomized, Controlled; Phase 2 Trial of Type 1 IFN Inhibitor Anifrolumab in Patients With Active Proliferative Lupus Nephritis. POS0690, EULAR 2021 Virtual Congress, 2–5 June.
2. Furie RA, et al. Lancet Rheumatol. 2019;1(4):e208-19.
3. Morand EF, et al. N engl J Med. 2020;382(3):211-21.

Systemic lupus erythematosus: increased risk of severe infection

Patients with systemic lupus erythematosus (SLE) have an increased risk of developing severe infections compared with non-SLE cases. Moreover, 21% of the mortality in SLE is related to these infections. These were the main outcomes of a first large population-based incident SLE cohort study [1].

Previous studies investigating the infection risk in SLE have been prevalent cohort studies with small sample sizes. The current study is a large, retrospective, 1:5 matched, incident cohort study based on 25 years of administrative data of 2 million randomly selected Canadian citizens. The authors identified 5,169 confirmed incident SLE cases (mean age 47; 90% women), who were matched for age and sex with 25,845 non-SLE individuals. Outcome measures were first severe infection (defined by the need for professional medical care) after SLE onset, the number of severe infections, and infection-related death.

The results demonstrated that SLE patients had an 82% increased risk of developing a severe infection compared with their matched non-SLE counterparts. Furthermore, SLE patients had twice as many severe infections and a 61% increased risk of infection-related death. Mr Kai Zhao (Simon Fraser University, Canada) argued that early SLE patients often have higher disease activity and use more glucocorticoids, factors that could explain the increased risk of severe infections. He suggested that a tailored treatment, including increased use of immunosuppressants, could provide a solution for this problem. In addition, further analysis of infection type (bacterial, viral) might give more insight into how to tackle severe infections in SLE in the future.

1. Zhao K, et al. Increased risk of severe infections and mortality in patients with newly diagnosed systemic lupus erythematosus: A population-based study. OP0043, EULAR 2021 Virtual Congress, 2–5 June.

Juvenile Idiopathic Arthritis and Osteoarthritis

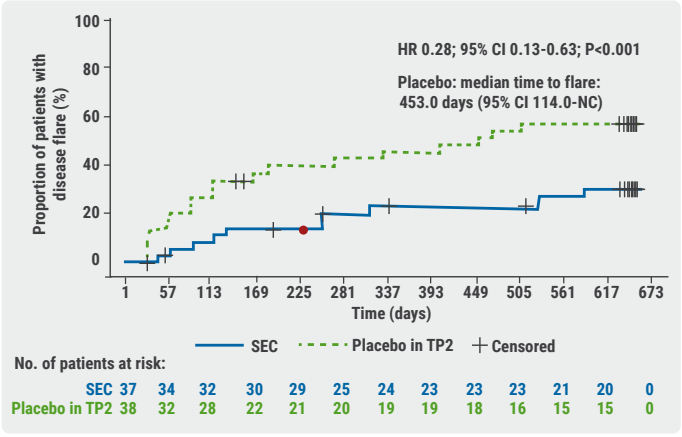
Efficacy and safety of secukinumab in juvenile idiopathic arthritis

Secukinumab significantly increased the time to flare and reduced the number of flares in children with enthesitis-related arthritis (ERA) and juvenile psoriatic arthritis (JPsA) compared with placebo. The safety profile of secukinumab in this population is congruent with the known safety profile of the drug. These were the main results of the phase 3w randomised, double-blind JUNIPERA trial 104 weeks after treatment initiation [1].

Efficacy and safety of secukinumab, a human monoclonal antibody targeting IL-17, has been demonstrated in adult patients with PsA and radiographic and non-radiographic axial spondyloarthritis [2-4]. JUNIPERA (NCT03031782) aimed to evaluate the efficacy and safety of secukinumab in ERA and JPsA patients (aged 2–18) with a history of inadequate response or intolerance to ≥1 NSAID or ≥1 DMARD. If patients (n=86) reached juvenile idiopathic arthritis (JIA)-ACR30 at the end of a 12-week open-label secukinumab 75/150 mg subcutaneous first treatment period (every week first 4 weeks, then every 4 weeks), they were randomised to secukinumab every 4 weeks (n=37) or placebo (n=38). After the occurrence of a flare in the second treatment period, the patient was moved to another open-label secukinumab treatment period. The primary endpoint was time to disease flare of patients on secukinumab versus placebo in the second treatment period.

Time to flare was significantly longer in the secukinumab arm compared with the placebo arm (HR 0.28; 95% CI 0.13-0.63; P<0.001) (see Figure).

Figure: Primary endpoint of time to disease flare for secukinumab versus placebo [1]



SEC, secukinumab; TP, treatment period.

The number of flares was lower in the treatment arm (secukinumab 10 vs placebo 21) and JIA-ACR30 was maintained more often for secukinumab-treated patients (89.2%) than for placebo patients (64.9%) after the second treatment period. Dr Nicola Ruperto (IRCCS Istituto G. Gaslini, Italy) argued that the median time to flare of 453 days in the placebo arm indicated a prolonged biological effect of the first treatment period. Complete resolution of enthesitis occurred in 73.9% of the ERA patients after the first treatment period. Adverse events (AEs) were reported in 91.7% of the secukinumab patients and 92.1% of the placebo patients, including 7 and 4 non-fatal serious AEs, respectively.

These findings also support the close pathophysiological link between ERA and adult spondyloarthropathy pattern arthritis where IL-17 blockers are also effective.

1. Ruperto N, et al. Efficacy and Safety of Secukinumab in Enthesitis-related Arthritis and Juvenile Psoriatic Arthritis: Primary Results from a Randomised, Double-blind; Placebo-controlled, Treatment Withdrawal; Phase 3 Study (JUNIPERA). LB0004, EULAR 2021 Virtual Congress, 2–5 June.
2. McInnes IB, et al. Lancet. 2015;386:1137–46.
3. Baeten D, et al. N Engl J Med. 2015;373:2534–48.
4. Deodhar A, et al. Arthritis Rheumatol. 2021;73:110–20.

Emerging therapies and future treatment directions in osteoarthritis

Many therapies for osteoarthritis (OA) have been investigated in recent years [1]. Sprifermin showed benefits in a subgroup with advanced disease. Results for lorecivivint were mixed, with the best results observed for an intermediate dose. Canakinumab had good efficacy, but an increased risk of infections.

Prof. Xavier Chevalier (University Paris-Est Créteil, France) discussed several recent trials investigating OA therapies [1]. First, he addressed a post-hoc analysis of the phase 2 FORWARD trial (NCT01919164), in which the efficacy of sprifermin was assessed in patients with knee OA [2]. Sprifermin is a recombinant form of fibroblast growth factor (FGF)18 and therefore a potent agonist of FGF receptor 2 and 3. The post-hoc analysis assessed the effects of sprifermin on an advanced disease subgroup (defined as medial or lateral minimum joint-space width (mJSW) 1.5–3.5 mm and WOMAC pain scores 40–90 units). A high dose of sprifermin (100 µg once every 6 months) had a higher effect on WOMAC pain scores compared with placebo at 3 years of treatment in the advanced disease subgroup (n=161). This effect was not found for the intention-to-treat (ITT) population (n=549). Moreover, total femorotibial joint cartilage thickness improvements in high-dose sprifermin participants were numerically higher in the advanced disease subgroup versus the ITT population. The advanced disease subgroup showed clinical and structural benefits of sprifermin administration. Therefore, this subgroup should be the target of future sprifermin trials, according to Prof. Chevalier.

Second, a phase 2 randomised placebo-controlled trial investigating the effects of Wnt inhibitor lorecivivint on pain and structural progression in knee OA was discussed [3]. A single 2 mL intra-articular injection of lorecivivint (0.03 mg, 0.07 mg, or 0.23 mg) was compared with placebo (n=114). At 52 weeks post injection, the results were mixed. The intermediate dose of lorecivivint (0.07 mg; n=117) showed

the best results in terms of pain reduction, represented by the difference between adjusted mean changes from baseline on WOMAC pain score (all participants: 2.4, P=0.405; unilateral symptomatic: 8.7, P=0.049; unilateral symptomatic without widespread pain: 11.2, P=0.025). A small structural effect was observed as well for the intermediate-dose group, represented as the difference between adjusted mean changes of medial joint space width (all participants: 0.06, P=0.529; unilateral symptomatic 0.39, P=0.021; unilateral symptomatic without widespread pain 0.42, P=0.032).

Third, an exploratory analysis of the CANTOS trial was discussed [4]. In this trial, 10,061 participants with high-sensitivity C-reactive protein and a history of myocardial infarction were included. Subjects were randomised to 50, 150, or 300 mg of IL-1β inhibitor canakinumab, administered subcutaneously every 3 months for a period of 5 years, or placebo. The exploratory study derived from CANTOS trial investigated the risk of total hip or knee joint replacement between the placebo and canakinumab arms. At a median of 3.7 years of follow-up, a remarkable reduction of 42% in total joint replacements was observed for the canakinumab recipients compared with placebo subjects. Prof. Chevalier noted that, although these results are highly interesting, the infection risk among canakinumab users was increased.

Prof. Chevalier argued that these trials reflect the individuality of OA treatment efficacy. "We should adapt to the specificity of a patient's profile. Many confounding factors influence treatment results in OA patients. Therefore, we need more evidence on therapy efficacy in patient subgroups." In addition, he argued that it is important to recruit the 30% of patients who show actual disease progression. "We should put more effort in recruiting these patients for future trials, based on features like repeated flares, pain, and accelerated cartilage loss." Prof. Chevalier concluded that treatment should probably be initiated earlier in the disease. "To obtain a disease-modifying effect of a pharmacological treatment, we should probably initiate when the first minimal changes on X-ray are being observed."

1. Chevalier X. WIN in OA clinical trials. EULAR 2021 Virtual Congress, 2–5 June.
2. Guehring H, et al. Semin Arthritis Rheum. 2021; 51(2):450-6.
3. Hochberg MC, et al. Arthritis Rheumatol. 2020; 72(10):1694-706.
4. Schieker M, et al. Ann Intern Med. 2020; 173(7):509-15.