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PEER-REVIEWED CONFERENCE REPORT

Vaccine Booster Improves Immune Response in Patients Treated with Rituximab

A late-breaking abstract assessed patients treated with rituximab and the efficacy of booster vaccination for protection against COVID-19 infection. Immune response was achieved in 94% of patients.

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Selective IL-23 Inhibition: A New Option in Active PsA

Results of the KEEPsAKE 1 and 2 trials demonstrated high efficacy of the IL-23 blocker risankizumab in adult patients with active psoriatic arthritis (PsA), independent of previous therapy. Risankizumab also showed an excellent safety profile.

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Promising Results for Gout Patients: New Xanthine Oxidase Inhibitor

Demonstrating efficacious serum urate-lowering in 156 gout patients with hyperuricemia, new phase 2 results for tigulixostat look promising.

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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 ACR Convergence 2021 was originally scheduled to take place at the Moscone Center in San Francisco, but decided to go 100% virtual because of the ongoing Coronavirus pandemic. Given the time of year, the famous city and the Southern Californian climate, it would be hard to generate virtual memories that could come anywhere near the experience of once boots on the ground in San Francisco.

That being said, the ACR in its own words attempted to deliver "groundbreaking science, innovative formats, live programming, networking, and flexible scheduling" and succeeded in doing so. With over 14,000 rheumatology professionals from >110 countries registering to hear over 300 speakers and over 2,000 abstracts, there was something for everyone.

Herein, we have briefly highlighted novel and interesting research across the breadth of the Rheumatic Diseases. Naturally, we have highlighted abstracts pertaining to COVID-19 from the rheumatology perspective and, reassuringly, the positive data that Rheumatology patients were mostly faring well during the pandemic continues to be the case nearly a year after the generation of the original data that was presented at the ACR in November 2021. One of our core activities involves the use of immunosuppression of B- and T-cell activity in the battle to restore immune homeostasis and unsurprisingly this can sometimes manifest as worse COVID-19 disease or inferior vaccination responses, and selected abstracts deal with this topic.

Moving from San Francisco to a famous New York Yankee quote, we also had a Rheumatological "déjà vu all over again" moment with evidence that very low dose rituximab, analogous to very low dose methotrexate, made the successful jump from cancer to rheumatoid arthritis. Lets hope that by the end of 2022 we can simply say that it is "all over" and we can return to meeting our colleagues face-to-face at the ACR.

Kind Regards,
Prof. Dennis McGonagle

Biography

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

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

Late-Breaking Abstracts

Vaccine booster improves immune response in patients treated with rituximab

Patients treated with rituximab have shown a reduced immune response after COVID-19 infections in previous studies. Therefore, the efficacy of a booster vaccine was assessed in a clinical study. Either a cellular or humoral immune response was achieved in 94% of patients, independent of the type of vaccine.

"B-cell depletion is an important treatment strategy in rheumatology," said Prof. Michael Bonelli (Medical University of Vienna, Austria) [1]. Yet, it puts patients at risk for severe COVID-19. Previous data has shown higher rates and longer duration of hospitalisation due to COVID-19 infections in these patients [2]. In addition, higher rates of severe COVID-19 infections were associated with therapy with rituximab compared with patients treated with TNF inhibitors [3]. Moreover, a 4 times higher mortality risk has been reported in patients treated with rituximab [4]. "One of the questions we raise is whether this was due to an insufficient vaccination response in patients treated with rituximab," Prof. Bonelli said. Previous studies have shown a reduced humoral immune response after vaccination in patients treated with rituximab compared with healthy controls. Roughly 30% of patients treated with rituximab develop neither humoral nor cellular immune response [5]. An important factor is the time between the last rituximab treatment and the vaccination, as a longer time span was associated with a higher level of antibodies. "If patients are clinically stable, we should consider postponing rituximab treatment to achieve a higher vaccination response," Prof. Bonelli suggested.

Prof. Bonelli and his team performed a randomised blinded study to compare the efficacy and safety of an additional booster vaccination with a vector versus mRNA vaccine in 60 patients treated with rituximab who did not seroconvert after a primary mRNA vaccination [1]. At baseline, participants were vaccinated with a third dose of either an mRNA vaccine or a vector vaccine. At week 4, seroconversion rates were comparable between vector (6 of 27 patients, 22%) and mRNA (9 of 28 patients, 32%) vaccines (P=0.6). Overall, 27% of patients seroconverted. Specific T-cell responses were achieved by all participants receiving a vector booster and by 81% in mRNA-vaccinated patients. Regarding the at-risk cohort, namely patients who neither developed a humoral nor a cellular immune response after standard vaccination, booster vaccination reduced this number from 31% to 6%. "Overall, in our case, 94% of patients on rituximab developed either a cellular or humoral immune response," Prof. Bonelli said. Vaccines were well tolerated with no severe adverse events.

According to these study results, Prof. Bonelli suggested that all older immunosuppressed patients should get an additional booster vaccination.

1. Bonelli M. Additional heterologous versus homologous booster vaccination in immunosuppressed patients without SARS-CoV-2 antibody seroconversion after primary mRNA vaccination: a randomized controlled trial. Abstract L17, ACR Convergence 2021, 03–10 November.
2. Felten R, et al. Ann Rheum Dis 2021 Sep 23;annrheumdis-2021-220549.
3. Spark JA, et al. Ann Rheum Dis 2021;80:1137-46.
4. Strangfeld A, et al. Ann Rheum Dis 2021;80:930-42.
5. Mrak D, et al. Ann Rheum Dis 2021 Oct;80(10):1345-1350.

IL-17 inhibition showing efficacy in GCA in phase 2 trials

The IL-17 inhibitor secukinumab showed efficacy in giant cell arteritis (GCA) in a phase 2 trial. The drug will now be investigated in a phase 3 trial towards defining a future role in disease.

"Experimental and pre-clinical data points to the fact that IL-17A has a role in the pathogenesis of GCA," Prof. Jens Thiel (Medical University Graz, Austria) stated [1]. This was the rationale to perform the phase 2 TitAIN trial (EudraCT 2018-002610-12), the first randomised, parallel-group, double-blind, placebo-controlled, multicentre trial of secukinumab in patients with GCA. Included participants had new-onset or relapsing GCA and were naïve to biological therapy. They were randomised to secukinumab 300 mg (n=27) or placebo (n=25), initially administered weekly for 5 weeks and then every 4 weeks through week 48 (last dose), in combination with a 26-week prednisolone taper regimen starting from baseline. Primary endpoint was the proportion of patients in sustained remission until week 28.

At week 28, 70.1% (95% CI 51.6–84.9) of participants receiving secukinumab were in sustained remission compared with 20.3% (95% CI 12.4–30) of those given placebo. Prof. Thiel pointed out that participants treated with secukinumab had a 9.3 times higher

chance of being in sustained remission at week 28 compared with placebo. The positive effect was maintained until week 53. At this time, 59.3% (95% CI 38.8–77.6) in the secukinumab group were still in remission compared with only 8.0% (95% CI 1.0–26.0) of those in the placebo group. The median time to flare among patients in the placebo group was 197 days (95% CI 101–280); the median time to flare in the secukinumab group was not reached because there were very few flare events through week 52. Cumulative prednisolone doses were similar in both groups at week 28, but the cumulative dose was higher in the placebo group by week 52 (3,376 mg vs 2,841 mg).

The safety profile of secukinumab was consistent with previous reports. There was 1 fatal serious adverse event in the secukinumab group and 1 in the placebo group. The event in the secukinumab group was regarded as unrelated to the treatment.

"If you look back some years, nobody would have expected that IL-17 inhibition could play a role in GCA, but you can learn a lot from basic immunology. Our hypothesis was that IL-17 has a major effect on the different immune cells in GCA and our data tell us this is really the case," Prof. Thiel concluded. A phase 3 trial is now being performed to determine whether these preliminary findings can be replicated and then adding anti IL-17A therapy to the GCA therapeutic armamentarium.

Other interesting options in the pipeline

In a GCA mouse model, arterial wall lesional T cells were effectively suppressed through inhibition of Januse kinase (JAK)3 and JAK1. This was the rationale for a pilot study (NCT03026504), presented as a poster during the meeting, in which 14 patients with GCA were treated with the JAK1/JAK2 inhibitor baricitinib (4 mg daily) for 52 weeks [2]. The agent was well tolerated, and only 1 patient relapsed during the study. The remaining 13 patients achieved steroid discontinuation and remained in disease remission until the end of the study. Another JAK1/JAK2 inhibitor, upadacitinib, is also under investigation in the SELECT-GCA trial (NCT03725202), enrolling a desired 420 participants in a multicentre, randomised, double-blind, placebo-controlled study over 4 years. So, the future looks bright for patients with GCA [3].

1. Venhoff N, et al. Secukinumab in giant cell arteritis: a randomized, parallel-group, double-blind, placebo-controlled, multicenter phase 2 trial. Abstract L19, ACR Convergence 2021, 03–10 November.
2. Koster M, et al. Baricitinib in relapsing giant cell arteritis: a prospective open-label single-institution study. Abstract 1396, ACR Convergence 2021, 03–10 November.
3. Harrington R, et al. Biologics. 2021 Jan 6;15:17-29.

Spotlight on Rheumatoid Arthritis

Cycling JAK inhibitors shows similar effectiveness to switching to a bDMARD in difficult-to-treat RA

The JAK-pot cohort study revealed that people with difficult-to-treat rheumatoid arthritis (RA) who do not have success with one Janus kinase (JAK) inhibitor could achieve success either by cycling to other JAK inhibitor medications or switching to a biologic drug. With both regimens, control of disease activity could be achieved to a similar extent.

More and more JAK inhibitors are entering the therapeutic arena.* Therefore, it is possible to use a second JAK inhibitor if the first JAK inhibitor fails in patients with RA. "In real life, JAK inhibitors are being used primarily in patients who have already failed treatment with a biologic disease-modifying antirheumatic drug (bDMARD), and they have shown to be effective in these situations," Dr Manuel Pombo-Suarez (Hospital Clinico Universitario de Santiago De Compostela, Spain) explained. "Looking at the 2020 update of the EULAR management recommendations for patients with RA who have failed a biologic DMARD or first JAK inhibitor, recommendation is that treatment with another biologic or another JAK inhibitor should be considered" [1]. At the time of the publication, no study data was available on the use of a second JAK inhibitor after failure/intolerance of a first JAK inhibitor. The rationale for the JAK-pot study was to investigate the efficacy of cycling from one JAK inhibitor to a second and to compare this with the efficacy of switching from a JAK inhibitor to a biologic [2].

**In September, the FDA announced a safety concern regarding the use of JAK inhibitors: Based on a completed FDA review of a large, randomised safety clinical trial, the FDA concludes that there is an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death with the use of tofacitinib. In contrast to an earlier evaluation, an increased risk of blood clots and death has also been reported with the lower dose of tofacitinib. The FDA also requires new and updated warnings for baricitinib and upadacitinib. The risks of these agents has not been adequately evaluated, but since they share the same mechanism of action, FDA considers that these medicines may have similar risks (for more information, see https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death).*

This nested cohort study included prospectively collected data on 708 RA patients (data obtained from 14 national registries of the JAK-pot collaboration) who failed a first JAK inhibitor and were then treated with either a second JAK inhibitor (cycling) or a bDMARD (switching) in routine care. A total of 154 patients cycled and 554 switched. The researchers compared the effectiveness of both treatment strategies on drug retention and disease activity, measured by DAS28 disease activity scores, over 1 year after they started their second treatment. Patients cycling JAK were older, had RA for longer, had already received more bDMARDs, and had longer exposure to the first JAK inhibitor than those who switched. Monotherapy was more common, and discontinuation of the first JAK inhibitor was more common for safety reasons than lack of efficacy. "JAK inhibitor cyclers had a more difficult treatment profile than the others," Dr Pombo-Suarez commented.

After 2 years of follow-up, cycling and switching showed similar drug survival. However, the researchers noted an interesting, although not statistically significant, trend: patients who cycled were more likely to discontinue the second treatment when they originally stopped their first JAK inhibitor because of side effects rather than lack of efficacy.

Over time, DAS28 improved similarly in both the cycling and switching groups after 1 year. "This was precisely the goal of our study: to refine treatment options after failure/intolerance to a JAK inhibitor. We intend to provide an answer for a growing population of RA patients who have failed treatment to JAK inhibitors," said Dr Pombo-Suarez. "A limitation of our study is that most patients received tofacitinib. It will be interesting to see new JAK inhibitors included in the future," he said. The most important take-away is that the effectiveness of cycling to another JAK inhibitor is no different from that of switching to a bDMARD. "Cycling JAK inhibitors is kind of a desperate scenario, but this might change in the future," Dr Pombo-Suarez concluded.

1. Smolen JS, et al. Ann Rheum Dis 2020;79:685-99.
2. Pombo-Suarez M, et al. Effectiveness of Cycling JAKi Compared to Switching to bDMARD in patients who failed a first JAKi in an international collaboration of registries of rheumatoid arthritis patients (the JAK-pot Study). Abstract 1442, ACR Convergence 2021, 3–10 November.

Pre-existing heart failure affects safety of hydroxychloroquine in RA patients

Comparing methotrexate and hydroxychloroquine therapy for rheumatoid arthritis (RA) resulted in similar results for severe cardiovascular events or sudden cardiac death/ventricular arrhythmia. In case of a concomitant heart failure diagnosis, methotrexate appears to be a safer option in terms of mortality and cardiovascular events.

"In the US, hydroxychloroquine is commonly used as a first-line treatment in patients with RA, while methotrexate is the recommended first-line disease-modifying antirheumatic drug (DMARD)," Dr Elvira D'Andrea (Brigham and Women's Hospital, MA, USA) stated [1]. In the wake of assessments on hydroxychloroquine use in COVID-19 patients, concerns regarding cardiovascular safety have been raised [2]. "We conducted a comprehensive cardiovascular safety evaluation of hydroxychloroquine compared with methotrexate in patients with RA," Dr D'Andrea explained the aim of the presented research [1].

Data from Medicare linked to the National Death Index was used to identify a cohort of patients with RA starting on their first-line medication with either hydroxychloroquine or methotrexate. This led to 54,462 matched pairs in each group that were followed over a median time of 209 days. The composite primary outcome was defined as sudden cardiac arrest or ventricular arrhythmia and 3-point major adverse cardiovascular event. Secondary outcomes consisted of cardiovascular events as well as all-cause mortality, myocardial infarction, stroke, and hospitalised heart failure. The mean age of the cohort was 74.3 years, and 78.5% were women. Heart failure was known in 12% of the cases, and coronary artery disease in just over 24%.

In terms of the primary outcome, no significant difference was found between methotrexate (i.e. reference group) and hydroxychloroquine: HR 1.03 (95% CI 0.79–1.35) for sudden cardiac death/ventricular arrhythmia and HR 1.07 (95% CI 0.97–1.18) for major adverse cardiovascular events. The results for the secondary outcomes, however, revealed significant differences between the groups for cardiovascular and all-cause mortality. Patients treated with hydroxychloroquine had a 41% higher relative risk for heart failure hospitalisation and the HR for all-cause mortality was 1.10.

A subgroup analysis was additionally performed based on prior history of heart failure. No disparities were shown between methotrexate or hydroxychloroquine treatment in those without previously established heart failure, but they were found for hospitalisation due to heart failure (HR 1.63 in favour of methotrexate). "Hydroxychloroquine use appears to be associated with increased risk of major adverse

cardiovascular events, cardiovascular mortality, all-cause mortality, and myocardial infarction in patients with a history of heart failure. An increased risk of hospitalisation for heart failure was observed in new users of hydroxychloroquine regardless of prior history of heart failure," Dr D'Andrea said in her final remarks.

1. D'Andrea E. Cardiovascular risk of hydroxychloroquine in the treatment of a rheumatoid arthritis: a retrospective cohort study. Abstract L11, ACR Convergence 2021, 3–10 November.
2. Desmarais J, et al. Arthritis Rheumatol. 2021 Oct 26. Online ahead of print.

Patients with RA-associated interstitial lung disease benefit from antifibrotic agent

The TRAIL1 study is the first trial to demonstrate the efficacy and safety of pirfenidone in patients with rheumatoid arthritis (RA) and associated interstitial lung disease (ILD). In participants receiving the antifibrotic, lung function decline was slowed down, particularly in those with a usual interstitial pneumonia pattern at baseline.

Some patients with RA develop progressive fibrosing ILD, characterised by increasing fibrosis on high-resolution CT, a decline in lung function, worsening symptoms, and high mortality. Patients with RA have a lifetime risk of 7.7% for this complication, which is an 8-time higher relative risk to develop ILD compared with the general population [1]. Previously, the antifibrotic agent nintedanib has shown benefits in patients with autoimmune-associated ILD [2]. Up to now, no completed treatment trials exclusively for RA subjects with ILD exist. This was the rationale to perform the TRAIL1 (NCT02808871), a randomised, double-blinded, placebo-controlled, phase 2 study of tolerability and efficacy of the antifibrotic pirfenidone in patients with RA-associated ILD [3].

All included patients had to have ≥10% fibrosis on high-resolution CT but were not required to have documented progression. "The randomisation target was 270 participants, but the study was stopped due to slow recruitment exacerbated by the COVID-19 pandemic," Prof. Joshua J. Solomon (National Jewish Health, CO, USA) said. Therefore, only 123 patients were randomised. Of these, 63 were treated with pirfenidone and 60 with placebo. The average extent of fibrosis was 20%. The primary endpoint was the incidence of a composite of decline from baseline in percentage predicted force vital capacity (FVC%) of ≥10% or death during the 52-week treatment period.

Results showed that 11.1% of patients treated with pirfenidone achieved the primary endpoint compared with 15% in the placebo group (OR 0.67; P=0.48). Subjects treated with pirfenidone had a slower rate of decline in lung function, measured by estimated annual change in FVC. This benefit was particularly seen in participants with a baseline usual interstitial pneumonia pattern on HRCT. There was no significant difference in the rate of treatment-emergent serious adverse events.

Prof. Solomon concluded that although the trial was under-powered to detect a difference in the composite primary endpoint, pirfenidone showed no new safety signals and slowed the decline of FVC over time in subjects with RA-ILD. The beneficial effect was more pronounced in those with a usual interstitial pneumonia pattern on baseline HRCT.

1. Bongartz T, et al. Arthritis Rheum. 2010 Jun;62(6):1583–91.
2. Flaherty KR, et al. New Engl J Med 2019;381:1718-27.
3. Solomon JJ, et al. A randomized, double-blinded, placebo-controlled, phase 2 study of safety, tolerability and efficacy of pirfenidone in patients with rheumatoid arthritis interstitial lung disease. Abstract L10. ACR Convergence 2021, 3–10 November.

Ultra-low dosing of rituximab in RA is a viable treatment option

Rituximab showed non-inferior efficacy of longer-term treatment of rheumatoid arthritis (RA) with an ultra-low dose. Dosing regimens of 500 mg and 200 mg led to comparable results to the 1,000 mg dose when following patients for up to 4 years.

As rituximab was originally developed for lymphoma, special dose-finding investigations for RA are limited [1]. "The optimal dose of rituximab in RA is unknown," said Mr Nathan den Broeder (Sint Maartenskliniek, the Netherlands) [1]. It has been however demonstrated that a low dose of 1,000 mg (or 2x500 mg) is equivalent to the registered high dose of 2x1,000 mg per 6 months [2]. Furthermore, the previous REDO trial (NTR6117) data showed on intention-to-treat analysis that an ultra-low dose of rituximab (i.e. 500 mg and 200 mg) was non-inferior to a standard low dose (1,000 mg) at 6 months, although the same conclusion failed in per-protocol analysis. Long-term data is lacking however. An extension trial of up to 4 years aimed to close this knowledge gap.

Of 142 patients in REDO, 118 entered the extension study that included outcomes like disease activity (using DAS28-CRP), quality of life, and adverse events. The mean age of the study participants was 64 years and 66% were women.

The disease duration was about 14 years and approximately 90% were positive for rheumatoid factor or anti-citrullinated protein antibody (ACPA). The mean follow-up of 3.2 years equalled 377 evaluated patient years. The study treatment was decided by the treating rheumatologist and was either 1,000 mg, 500 mg, or 200 mg rituximab. Patients who had a good response in the REDO trial were encouraged to continue on ultra-low dosing. Of note, only 7 patients were switched to a different disease-modifying antirheumatic drug (DMARD) during the trial.

With regard to disease activity, both ultra-low dose groups demonstrated non-inferiority to the 1,000 mg group (non-inferiority margin 0.6). Interestingly, the analysis on received dose that was adjusted for medication use and rheumatoid factor/ACPA-positivity revealed only a slightly higher DAS28-CRP in the ultra-low dosing group. Overall, the median yearly dose that patients received in the trial was 978 mg. At the end, dosing intervals were all around 6 months and the final dosage of rituximab was 200 mg in 31% of patients, 500 mg in 40%, and 1,000 mg in 29% of participants.

Adverse events, most commonly infections and planned surgeries, were similar between groups. The lower infection rate on ultra-low-dose rituximab that was seen in REDO was not confirmed in this extension trial. However, the researchers believe there has been a lot of underreporting as adverse events were not as closely followed as in REDO.

"In summary, I believe we can conclude that ultra-low-dose rituximab is a good option for patients responding well to 1,000 mg of rituximab," Mr den Broeder stressed.

1. Den Broeder N. Long-term effectiveness of ultra-low doses of rituximab in rheumatoid arthritis. Abstract 1443, ACR Convergence 2021, 3–10 November.
2. Bredemeier M, et al. Clin Rheumatol. 2015 Oct;34(10):1801-5.

Kidney disease and hydroxychloroquine dose are risk factors for developing retinopathy

Long-term use and high-dose treatment were among the independent risk factors that distinctly augment the risk of retinopathy for patients with systemic lupus or other rheumatoid diseases treated with hydroxychloroquine. Another risk factor is comorbid chronic kidney disease, which nearly doubled the retinopathy risk.

Previous findings suggested a 5 times higher risk for retinopathy in patients within the first 10 years of hydroxychloroquine treatment when treated with 5 mg/kg/day; thus, guidelines recommend to not pass this threshold [1,2]. To identify risk factors for hydroxychloroquine retinopathy, Dr April Jorge (Massachusetts General Hospital, MA, USA) and colleagues obtained data from the Kaiser Permanente Northern California consortium to ascertain a large cohort of 4,899 subjects with systemic lupus erythematosus or other rheumatoid diseases with incident hydroxychloroquine use of ≥5 years between 1997 and 2020 [3].

All participants had at least 1 Spectral-Domain Optical Coherence Tomography (SD-OCT) scan after 5 years of treatment. Each SD-OCT was reviewed by an expert ophthalmologist who graded existing hydroxychloroquine retinopathy into mild, moderate, or severe. A second expert evaluation was done for all pathologies and a sample of normal findings. Cases were matched by age, sex, and time of the first start on hydroxychloroquine with up to 5 controls.

"The main exposure of interest was hydroxychloroquine use, and a key strength of this study was that we utilised pharmacy dispensing records to obtain detailed information of hydroxychloroquine dose and the duration of use, and we assessed the dose in mg per day and weight-based dosing in mg per kg of body weight per day," highlighted Dr Jorge. Candidate risk factors included age, sex, weight, diabetes, chronic kidney disease, and medication with other retinal toxins.

Among nearly 5,000 incident users, 164 cases of hydroxychloroquine retinopathy were found, of which 100 were mild in severity, 38 moderate, and 26 severe; 80% of the cases were subclassified as having the typical parafoveal and 20% the pericentral pattern. In this nested case-control study, the mean age was 56, and over 90% were women; 48% of participants took hydroxychloroquine for rheumatoid arthritis, followed by 16% due to systemic lupus erythematosus.

A conditional logistic regression identified various risk factors for retinopathy. "We observed a dose-response relationship with an increase in odds of retinopathy associated with increased weight-based dosing category. Using ≤4 mg/kg as the reference group: the odds ratio ranged from 2.76 for a dose between 4 to 5 mg/kg up to 7.36 for using ≥6 mg/kg/day," stated Dr Jorge. She added that there were also increased odds (OR 2.96) with each additional 100 mg/day and each 5 years of use. Moreover, chronic kidney disease (≥stage 3) about doubled the odds of retinopathy. "Patients with these additional risk factors may warrant closer

monitoring and this should also be a consideration when prescribing medication," Dr Jorge recommended.

1. Melles RB, et al. JAMA Ophthalmol. 2014 Dec;132(12):1453-60.
2. Fanouriakis A, et al. Ann Rheum Dis. 2019 Jun;78(6):736-745.
3. Jorge A. Risk factors for hydroxychloroquine retinopathy and its subtypes – prospective adjudication analysis of 4,899 incident users. Abstract 0989, ACR Convergence 2021, 03–10 November.

More pros than cons for the use of statins in RA

RA patients benefit from significant reductions in cardiovascular and all-cause mortality when treated with statins. The advantages of statin treatment outweigh the modest risk of diabetes resulting from the therapy.

"Only few studies so far have shown that statins improve endothelial function, atherosclerotic plaques, and even disease activity in patients with RA. Few studies also showed that statins can reduce cardiovascular disease and all-cause mortality in RA with a wide range of magnitude," Dr Gulsen Ozen (University of Nebraska Medical Center, NE, USA) pointed out [1]. Unlike for the general population, data on the type 2 diabetes mellitus (T2DM) risk associated with statin use is still limited in RA patients. "As we know, T2DM is an important concern in RA, because it not only increases and worsens cardiovascular outcomes but also some infection and cancer incidences and outcomes which are other causes of mortality in RA," underlined Dr Ozen.

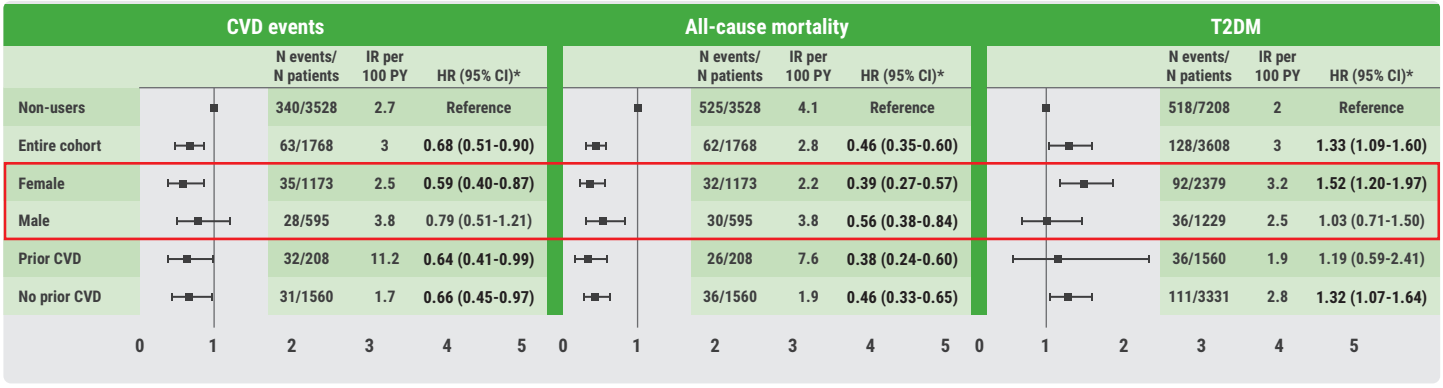
To assess the risk/benefit profile of statin medication regarding mortality, cardiovascular disease, and T2DM of patients with RA, Dr Ozen and her colleagues performed an observational study, utilising 3 large databases: UK Clinical Practice Research Datalink, Hospital Episode Statistics, and Office of National Statistics. Included were 1,768 statin initiators and 3,528 matched non-users for the assessment of cardiovascular disease and all-cause mortality, along with 3,608 statin users and 7,208 propensity-matched non-users for the evaluation of T2DM in RA. The mean age within the cohorts was 65 years, and the mean duration of RA was 4–5 years.

In the entire cohort, statin use was significantly linked to a decrease of 32% in cardiovascular events and a 54% decrease in all-cause mortality on the one hand, and a 33% elevated risk of T2DM (see Figure). "We assessed patients with or without cardiovascular disease, and we found that both groups had similar cardiovascular event reduction, all-cause mortality reduction, and T2DM risk increase with statins. However, only the diabetes risk significantly increased in patients without prior vascular disease," Dr Ozen elaborated. She also highlighted that the numbers needed to prevent 1 cardiovascular event or 1 death from any cause by 1 year of statin treatment were 102 or 42, respectively, whereas 127 persons would have to be exposed to statins over the same period, to cause 1 new onset of T2DM.

"Given that statins are still underutilised in patients with RA, our findings emphasise the statin initiation in eligible patients with monitoring for T2DM while on treatment. As statins may have potential pleotropic and anti-inflammatory effects, they may be offering further benefits on other causes of mortality in RA," Dr Ozen concluded.

1. Ozen G. Reduction of cardiovascular disease and mortality versus risk of new onset diabetes with statin use in patients with rheumatoid arthritis. Abstract 1427, ACR Convergence 2021, 03–10 November.

Figure: Association between the initiation of statin use and various outcomes (as treated analysis) [1]



*Due to imbalance in time-conditional propensity score matching, hazard ratios are adjusted for age, gender, deciles of propensity score, aspirin, beta-blockers, ACB/ARBs, cerebrovascular disease, thiazide diuretics, diabetes and its medications with the latter 3 only for CVD and mortality

Psoriatic Arthritis: Novel Developments

Selective IL-23 inhibition: a new option in active PsA

Results of the KEEPsAKE 1 and 2 trials demonstrated high efficacy of the IL-23 blocker risankizumab in adult patients with active psoriatic arthritis (PsA), independent of previous therapy. Risankizumab also showed an excellent safety profile.

The selective IL-23 inhibitor risankizumab has already been approved for moderate-to-severe psoriasis and is being investigated as a treatment for adults with PsA. At the ACR meeting, 2 presentations covered the phase 3 KEEPsAKE trials, which compared risankizumab with placebo [1,2].

In a plenary session, Prof. Andrew Östör (Monash University, Australia) presented an integrated analysis of data from the KEEPsAKE 1 (NCT03675308) and KEEPsAKE 2 (NCT03671148) studies, including 1,407 patients with active PsA who had inadequate response or intolerance to either ≥1 csDMARDs (KEEPsAKE1) or bDMARDs (KEEPsAKE2). In both trials, patients were randomised (1:1) to receive blinded subcutaneous risankizumab 150 mg (n=707) or placebo (n=700) at weeks 0, 4, and 16. Prof. Östör pointed out the high burden of disability and fatigue in the study population. The primary endpoint for this pooled analysis was the proportion of patients achieving 20% improvement in the ACR20 at week 24.

The primary endpoint was met by 55.5% of patients in the risankizumab group versus 31.3% in the placebo arm, a highly statistically significant difference (P<0.001). Moreover, risankizumab showed significant improvements compared with placebo in all secondary clinical and patient-reported outcomes, e.g. in ACR50 (31.2 vs 10.6%) and ACR70 (14.1 vs 5.0%) response rates. In addition, 53.2% of patients treated with risankizumab compared with 10% in the placebo arm achieved almost a clearance of psoriatic skin lesions (assessed as a 90% improvement of the Psoriasis Area and Severity Index). Superiority was also demonstrated in the physical function, assessed with the Health Assessment Questionnaire Disability Index (HAQ-DI).

Treatment-emergent adverse events (AEs) were noted in 45.5% of patients in the risankizumab group and 43.9% of those given placebo. Serious treatment-emergent AEs were seen in 3% of patients in the risankizumab arm and 4.4% in the placebo arm. So, overall risankizumab was well tolerated with a similar safety profile that is known from psoriasis trials and is the second p19 IL-23 blocker, following guselkumab, to show efficacy in phase 3 PsA trials.

1. Östör A, et al. Efficacy and Safety of Risankizumab for Active Psoriatic Arthritis: 24-Week Integrated Results from 2 Phase 3, Randomized, Double-blind Clinical Trials for CsDMARD-IR and Bio-IR Patients. Abstract 0453, ACR Convergence 2021, 3–10 November.
2. Lidar M, et al. Efficacy and Safety of Risankizumab for Active Psoriatic Arthritis: 24-Week Results from the Phase 3, Randomized, Double-blind Clinical Trial for CsDMARD-IR and Bio-IR Patients. Abstract 0183, ACR Convergence 2021, 3–10 November.

Ustekinumab: highly efficacious in PSA independent of methotrexate

Monotherapy with the IL-12/23 blocker ustekinumab demonstrated equal efficacy in patients with active psoriatic arthritis (PsA) compared with the combination of methotrexate and ustekinumab. In contrast, the addition of methotrexate was responsible for more side effects and did not enhance efficacy or quality of life in these patients.

Although biologics like tumour necrosis factor (TNF) inhibitors or cytokine blockers are the most effective agents in treating active PsA, randomised clinical trials usually require treatment failure or intolerance of conventional disease-modifying antirheumatic drug (DMARDs)/methotrexate before initiation of a biological treatment. In most countries, biologics can only be prescribed in patients not responding to previous conventional therapy with DMARDs. Methotrexate is often used as a first-line agent in these patients. “The value of methotrexate together with biologic DMARDs is still unclear in PsA,” said Dr Michaela Köhm (Goethe-University Frankfurt, Germany). Therefore, Dr Köhm and her team designed an investigator-initiated, randomised, placebo-controlled trial in active PsA to examine whether treatment outcomes with ustekinumab in combination with methotrexate (either newly initiated or ongoing) differ from ustekinumab monotherapy [1].

In total, 173 patients with active PsA were randomised to ustekinumab with methotrexate or ustekinumab with placebo. Baseline data were well balanced between treatment groups.

Baseline differences were only seen in dactylitis (24.1% vs 19.0%), body surface area (BSA; 2.9% vs 1.0%), and quality of life, assessed in the Dermatology Life Quality Index (8.6 vs 6.9).

At week 24, the mean DAS28-ESR disease activity score decreased by 1.7 points for both the combination and for ustekinumab plus placebo groups. Changes in other outcomes at week 24 were also similar between groups. The effect of blinded initiation or withdrawal of methotrexate on ustekinumab efficacy was also explored in subgroups of patients who were treatment-naïve or pre-treated with methotrexate, respectively. Again, adding methotrexate had no significant impact in 24 weeks. Patients that received methotrexate together with ustekinumab experienced 18% more adverse events and the only 2 serious infections documented in this study.

The authors concluded that ustekinumab is an effective treatment for active PsA, independent of methotrexate use. As the latter has no positive impact on efficacy for arthritis, enthesitis, dactylitis, skin, quality of life, and function, there is no evidence to either add methotrexate or maintain ongoing methotrexate when starting ustekinumab.

1. Köhm M, et al. Neither add-on nor withdrawal of methotrexate impacts efficacy of IL12/23 inhibition in active PsA: data from a multicenter investigator-initiated randomized placebo-controlled clinical trial on arthritis, dactylitis, enthesitis, psoriasis, QoL and function. Abstract L12, ACR Convergence 2021, 3–10 November.

COVID-19: What You Need to Know

Vaccinated rheumatic patients carry increased risk for COVID-19 breakthrough infections

Compared with the general population, breakthrough infections after COVID-19 vaccination happen more often in patients who suffer from autoimmune or inflammatory rheumatic diseases. The risk of infection is affected by the type of medication and pre-existing diagnosis.

"COVID-19 vaccines are highly effective in the general population, but we also know that in certain populations, such as elderly and severely immunocompromised, they may have reduced effectiveness," Prof. Jasvinder Singh (University of Alabama at Birmingham, AL, USA) explained [1]. For certain drug classes, like glucocorticoids and B-cell depleting agents, a reduction in antibody response has already been found, but much is unknown about other treatments and rheumatic diseases [2]. Therefore, the current study aimed to investigate the possibility of an increased risk for breakthrough infection after COVID-19 vaccination in patients with autoimmune or inflammatory rheumatic diseases [1]. Data from the National COVID Cohort Collaborative served as the source for the investigation, providing a sample of 577,335 vaccinated people, of whom 47,303 had a rheumatic disease. An incident COVID-19 diagnosis that occurred at least 14 days after vaccination was defined as a breakthrough infection.

Overall, the median age within the cohort was 48 years, 58% were women, 58% White, 18% Hispanic, and 11% Black. Over 90% were fully vaccinated, most of them (around 70%) with the Pfizer-BioNTech vaccine. The rate of breakthrough infections in people without rheumatic disease was 3%. The prevalence in those with rheumatic disease ranged from 3.3% in lupus to 4.5% in rheumatoid arthritis, and 4.7% in polymyalgia rheumatica. In the subgroup that received Pfizer-BioNTech, this translated into a crude prevalence rate of 31.2/1,000 persons in the patients without rheumatic disease versus 41.5/1,000 patients with rheumatic disease. Taking subjects without rheumatic disease as a reference, significantly higher adjusted odds ratios for breakthrough infection were found for rheumatoid arthritis (OR 1.33; P<0.001), gout (OR 1.14; P=0.001), polymyositis (OR 1.97; P=0.018), polymyalgia rheumatica (OR 1.2; P=0.14), vasculitis (OR 1.19; P=0.004), and multiple rheumatic diseases (OR 1.17; P=0.011). Moreover, the researchers differentiated between various treatment drugs in comparison with no immunosuppressive medication. Significance was found for exposure to biologics, which was associated with an adjusted OR of 1.61 (P=0.002) and multiple autoimmune/rheumatic disease medications with a 38% higher likelihood of breakthrough infections (OR 1.38; P<0.001).

"This data, we believe, has important information and guide for patients, providers, and policymakers, and although more

research is needed to examine several important questions that our study generates, we still support the use of at least a third dose of COVID-19 vaccine for immunocompromised patients, including those with rheumatic or autoimmune diseases, or those getting medications that are associated with immunosuppression and continued use of other precautions," concluded Prof. Singh.

1. Deepak P, et al. Ann Intern Med. 2021 Nov;174(11):1572-1585.
2. Singh J. Breakthrough COVID-19 infections post-vaccination among immunocompromised patients with autoimmune or inflammatory rheumatic diseases: a retrospective cohort analysis from a U.S. Nationally-sampled Electronic Medical Record Data Repository. Abstract L16, ACR Convergence 2021, 03–10 November.

B-cell depleting medication increases COVID-19 breakthrough infection outcome risk

Nearly half of the rheumatic patients in need of hospitalisation for a SARS-CoV-2 infection after full vaccination were on treatment with CD20 inhibitors. Additional protective measures for this population at risk should be considered.

"COVID-19 vaccinations are recommended and usually well tolerated and efficacious among people with rheumatic disease. However, lab-based studies using surrogate markers of protection against COVID-19 have demonstrated reduced vaccine immunogenicity in people on certain immunosuppressant medications," Prof. Jean Liew (Boston University, MA, USA) explained the need for further knowledge to effectively counsel immunocompromised patients [1].

The current study analysed data from the Global Rheumatology Alliance registry to shed further light on this matter. The investigation included nearly 200 patients with SARS-CoV-2 infection after vaccination and their outcomes in terms of hospitalisation, the need for oxygen, and death. The 87 participants who were defined as fully vaccinated had received either a single vaccination (single-dose vaccine) or the second dose (2-dose series) at least 14 days before inclusion. The partially vaccinated (n=110) definition comprised patients with a single-dose vaccination within the previous 13 days or 1 dose of a 2-dose series ≥14 days before. Participants had a mean age of 53.2 years, 72.6% were women, and 55.3% White. Over 40% suffered from rheumatoid arthritis, 15.4% from systemic lupus erythematosus, and 9.6% had psoriatic arthritis. Treatment prior to vaccination included methotrexate (27.4%), leflunomide (6.6%), azathioprine (5.1%), mycophenolate (10.7%), TNF inhibitors (18.8%), CD20 inhibitors (11.2%), and JAK inhibitors (6.1%); 33% were on glucocorticoids. "Most common comorbidities were hypertension, obesity, and lung disease and the majority received mRNA vaccines," Prof. Liew indicated.

In general, 51 (25.9%) of the study participants were hospitalised and 9 (4.6%) died. In fully-vaccinated patients, of whom 28% were on glucocorticoids and 18% on CD20 inhibitors, the mean time to infection was 111.8 days. "All 4 individuals who required invasive ventilation, subsequently died, as well as 1 individual on non-invasive ventilation," stated Prof. Liew. Within the subgroup of fully-vaccinated patients who needed hospitalisation due to COVID-19, 45.5% received CD20 inhibitors for their rheumatic disease. "We did not find meaningful differences in glucocorticoid use among breakthrough infections by hospitalisation status, and we had few patients on other medications such as TNF inhibitors or methotrexate," Prof. Liew pointed out. Lung disease as a comorbidity was present in 36% of fully-vaccinated in-patients with a breakthrough infection.

"These findings support prior laboratory data that people on certain rheumatic disease medications, such as CD20 inhibitors and mycophenolate, may be at higher risk for poor outcomes of breakthrough SARS-CoV-2 infection versus the general population. So, additional risk mitigation strategies including additional vaccine doses, monoclonal antibody treatment, and possibly oral antivirals may be needed to protect this high-risk population," she concluded.

1. Liew JW. SARS-CoV-2 infections among vaccinated individuals with rheumatic disease: results from the COVID-19 Global Rheumatology Alliance provider registry. Abstract L04, ACR Convergence 2021, 3–10 November.

COVID-19 mRNA vaccine safe and tolerable in adults with autoimmune disease

A Canadian study revealed that the Moderna mRNA-1273 SARS-CoV-2 vaccine is safe in immunocompromised adults with autoimmune disease and not associated with severe disease flares. Interestingly, patients with rheumatoid arthritis (RA) ≥65 years had similar immune responses compared with younger patients.

Immunocompromised patients or those with a history of autoimmune disease have mainly been excluded from clinical vaccination trials against COVID-19. Therefore, a Canadian study (NCT04806113) assessed the safety and efficacy of 2 doses of the mRNA-1273 SARS-CoV-2 vaccine in patients with autoimmune diseases [1,2]. "Our study was designed as a prospective, randomised, open-label comparative trial

that was conducted at 2 centres," Dr Inés Colmegna (McGill University Health Centre, Canada) said. The safety of the vaccine was the primary outcome. The researchers also assessed the effect of age and medication on the safety and immunogenicity of the vaccine. "The design we used was the same design of the large phase 3 trials that led to the approval of the mRNA vaccine in the general population," Dr Colmegna explained.

Included participants had either seropositive RA on stable treatment for ≥3 months, systemic lupus erythematosus (SLE) on stable therapy with mycophenolate mofetil (MMF), or other rheumatic diseases receiving ≥10 mg of prednisone per day. These 3 groups were compared with age/sex-matched healthy controls. All in all, 220 patients were enrolled, including 131 RA patients, 23 SLE patients, 8 patients with other rheumatic diseases, and 58 controls. Local and systemic adverse events were more frequently reported after the second dose in all subjects (94% vs 86.8%). Pain at the injection site was the most common side effect. Disease activity scores post-vaccination did not increase in patients with rheumatic disease.

Regarding immunogenicity, controls fared substantially better than patients with autoimmune disease. After the first shot, positivity for serum IgG antibodies against SARS-CoV-2 spike protein and its receptor-binding domains was 100% in controls compared with only 67.7% in RA, 34.8% in SLE, and 87.5% in other rheumatic diseases. After the second dose, seropositivity remained 100% in controls, increased to 88.5% in RA and 78.3% in SLE, and persisted at 87.5% in other rheumatic diseases. Older patients with RA (>65 years) had a similar seropositivity post-second dose compared with younger patients (88% anti-Spike and anti-RBD positivity versus 88.8%). Patients treated with rituximab or MMF had lower humoral responses than patients not on those drugs (17.6% and 78.3% after the second dose, respectively).

"This study is reassuring in terms of the adverse event profile after complete vaccination of mRNA vaccines, specifically Moderna, in patients with autoimmune diseases," Dr Colmegna said. No serious adverse events were reported, and vaccination did not lead to severe disease flares. However, in RA patients on rituximab and SLE patients on MMF, reduced vaccine-induced humoral responses have to be expected. These data are consistent with the general efficacy of vaccination, albeit more nuanced in patients with autoimmune diseases.

1. Colmegna A, et al. COVID-19 vaccine in immunosuppressed adults with autoimmune diseases. Abstract L02, ACR Convergence 2021, 03–10 November.
2. Colmegna A. 6S229. Press conference: infectious & rare disease, ACR Convergence 2021, 03–10 November.

SLE Treatment: What Is New

Iberdomide: an upcoming new treatment possibility in lupus erythematosus

In an extension trial after the blinded phase 2 evaluation, iberdomide showed lasting benefits as a therapeutic agent for systemic lupus erythematosus (SLE). Safety assessments up to 1 year were reassuring.

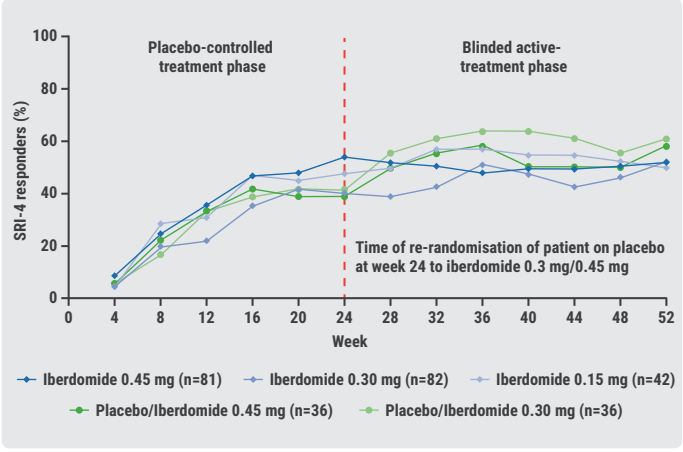
"Iberdomide is a high-affinity cereblon ligand that promotes degradation of 2 transcription factors: Ikaros and Aiolos. These factors are involved in immune-cell development, homeostasis, and genetic variants associated with risk for lupus," Prof. Joan Merrill (Oklahoma Medical Research Foundation, OK, USA), explained the properties of the study drug [1]. Gene polymorphisms of these transcription factors are associated with the risk of SLE and these transcription factors are overexpressed in the blood cells of patients with SLE [2–4].

In a previously published phase 2, randomised-controlled trial, oral iberdomide has been investigated for efficacy and safety in the treatment of SLE (NCT03161483) [5]. The 247 study subjects were randomised to placebo or iberdomide at daily doses of 0.45 mg, 0.30 mg, or 0.15 mg for the first 24 weeks. The primary endpoint was defined as SLE Responder Index (SRI)-4 response. Mean patient age was between 43.4 and 46.4 years, the vast majority of patients were women.

The primary endpoint at week 24 was met by 54.3% of those on the highest dose of iberdomide compared with 24.9% on placebo. In the novel extension trial, sustained efficacy and safety of iberdomide was investigated through week 52. The 80 patients on placebo were re-randomised to iberdomide 0.3 mg or 0.45 mg at week 24, while patients on iberdomide continued their original regimens [1].

Looking at the primary endpoint of SRI-4 at week 52, response rates were either sustained or improved from week 24 in all treatment groups, leading to 51.9% (0.45 mg), 52.4% (0.3 mg), and 50.0% (0.15 mg) of patients achieving this endpoint (see Figure). The percentage of patients in the former placebo group, who were switched to the study drug after week 24, also increased in SRI-4 achievement at week 52: 41.7% versus 61.1% (placebo to 0.3 mg) and 38.9% versus 58.3% (placebo to 0.45 mg). Furthermore, for SRI-6 and SRI-8 achievement in patients with a baseline SLE disease activity index 2,000 (SLEDAI 2K) ≥10, sustainment or ameliorations in efficacy were noted. "The tender and swollen joint count endpoint was not met by any dosing group by week 24, but it continued to improve in all groups between weeks 24–52. However, in the second half there is no ongoing placebo group to compare this to," Prof. Merrill explained.

Figure: SLE responder index 4 (SRI-4) response up to week 52 in the intent-to-treat population (non-responder imputation) [1]



Infections of the urinary tract (14.9%) or the upper respiratory tract (11.2%), as well as neutropaenia (9.8%) were the highest reported adverse events, with a suggestion of dose response for the latter 2. "The most frequent events leading to discontinuation were rash and neutropaenia," Prof. Merrill said. Iberdomide was overall well tolerated.

"In conclusion, iberdomide treatment of patients with lupus was associated with sustained clinical benefits in multiple measures of disease activity up to week 52," Prof. Merrill summarised.

1. Merrill J. Sustained Efficacy and Safety of Iberdomide to Week 52 in Patients with Active Systemic Lupus Erythematosus (SLE) in a Phase 2, Randomized, Placebo-Controlled Study. Abstract 1458, ACR Convergence 2021, 3–10 November.
2. Westra H-J, et al. Nat Genet 2013;45:1238-1243.
3. Lessard CJ, et al. Am J Human Genet. 2012;90:648-660.
4. Nakayama Y, et al. J Immunol 2017;199:2388-2407.
5. Merrill J, et al. Arthritis Rheumatol. 2020;72 (suppl 10).

Sequential rituximab after belimumab does not improve disease control in SLE

A single cycle of rituximab after therapy with belimumab did not improve disease control or remission in patients with active systemic lupus erythematosus (SLE). This was the disappointing main result of the BLISS-BELIEVE study.

"Given a potential synergistic mode of action, belimumab and rituximab combination therapy may enhance clinical benefit in SLE patients," Prof. Cynthia Aranow (Feinstein Institutes for Medical Research, NY, USA) explained [1]. This could be of importance since disease control remains an unmet need in SLE. The objective of the double-blind, placebo-controlled, 104-week, phase 3 study BLISS-BELIEVE (NCT03312907) was to assess the efficacy and safety of sequential therapy with belimumab followed by a single rituximab cycle in patients with SLE.

Thus, patients with active SLE received subcutaneous belimumab once weekly for 52 weeks and were randomised 1:2:1 to receive additionally: placebo at weeks 4 and 6 (group A), rituximab in a dose of 1,000 mg intravenous at weeks 4 and 6 (group B), or standard therapy for 104 weeks (group C). Group A and B discontinued immunosuppressants by week 4. A 52-week observation therapy followed the 52-week treatment phase in groups A and B. The primary study endpoint was the percentage of patients with disease control (assessed as SLE Disease Activity Index score 2,000 [SLEDAI-2K] without other immunosuppressants and prednisone-equivalent dose of ≤5 mg/day) at week 52. As Prof. Aranow pointed out, the primary comparison was between groups A and B, group C was included for reference comparison only.

Overall, 19.4% of patients in group A, 18.8% in group B, and 19.7% in group C discontinued belimumab treatment by week 52 mainly due to adverse events. No statistically significant differences were detected between group A and B in the proportions of patients with disease control at week 52, clinical remission at week 64, and disease control at week 104. Duration of disease control was significantly higher in group B than group A at week 52. At this time, anti-dsDNA positive patients at baseline achieved a significant decrease from baseline in anti-dsDNA when treated with belimumab followed by rituximab than with belimumab followed by placebo.

Regarding safety, more serious infections were reported in group B. "In conclusion, compared with belimumab alone, sequential therapy did not improve disease control or

remission, although the duration of disease control at week 52 and SLEDAI-2K reductions at weeks 1 and 4 were greater," Prof. Aranow said. In addition, more serious infections were seen in patients using belimumab rituximab sequential therapy. "Using new clinical endpoints underscores the efficacy of belimumab for disease control," Prof. Aranow concluded.

1. Aranow C, et al. Efficacy and safety of subcutaneous belimumab (BEL) and rituximab (RTX) sequential therapy in patients with systemic lupus erythematosus: the phase 3, randomized, placebo-controlled BLISS-BELIEVE Study. Abstract L13, ACR Convergence 2021, 3–10 November.

Lupus patients less protected by COVID-19 vaccine

Nearly 30% of patients with lupus had an inadequate response to the new COVID-19 vaccines as measured by ELISA for SARS-CoV-2 spike protein receptor-binding domain. Lower vaccine response was associated with the use of prednisone, immunosuppressants, or mycophenolate mofetil, whereas patients taking anti-malarials showed an almost 12-times improved response. Overall disease activity did not change after vaccination.

Phase 3 clinical trials of all 3 COVID-19 vaccines excluded patients on immunosuppressants or immune-modifying drugs within 6 months of enrolment, so there is little data on the immunogenicity of SLE patients. "Many of us in the rheumatology community have been working on addressing the question of whether certain immunosuppressive medications affect the response to the new COVID-19 vaccines," said Dr Peter Izmirly (New York University Grossman School of Medicine, NY, USA). This is particularly important because some people with lupus have been hesitant about getting vaccinated for fear of a disease flare. "Our group has previously shown that after natural infection with SARS-CoV-2, most lupus patients developed and maintained a serologic response to the virus," Dr Izmirly explained.

The current study explored the serological response and the development of SLE flares among a group of a multi-ethnic/racial SLE patient cohort (n=90) compared with 20 healthy controls after COVID-19 vaccination [1]. "We decided to limit our study to only patients with SLE to assess both the medications and disease effect on the response to the vaccine and to assess any change in disease activity post-vaccination." All patients in the study received a complete COVID-19 vaccine schedule. IgG seroreactivity to the SARS-CoV-2 spike receptor-binding domain and SARS-CoV-2 microneutralisation were used to evaluate B-cell response to the vaccine, while T-cell response was assessed by ELISpot through IFN-gamma production.

In general, patients with SLE had lower mean antibody titres after vaccination compared with healthy patients. Researchers found that 26 (29%) SLE patients developed an IgG antibody response to the SARS-CoV-2 spike receptor-binding domain, which fell below the lowest response obtained for the controls. In bivariate analysis, lower vaccine response was associated with the use of prednisone or immunosuppressants. In contrast, taking anti-malarial drugs was associated with a more positive response to the vaccine. In addition, having normal anti-dsDNA antibodies before vaccination was associated with a low vaccine response (see Table). An analysis including only those patients who were on any immunosuppressants confirmed the association of a normal anti-dsDNA antibody with poor response.

Table: Predictors for low vaccine response in SLE patients in a logistic regression analysis [1]

Predictor variable	Adjusted OR (95% CI)	P-value
Being on any immunosuppression other than antimalarials	15.4 (2.8-82.3)	0.002
Normal anti-dsDNA antibody prior to vaccination	14.5 (2.20-82.3)	0.006
Lower platelet value (50×10^9 cells/L decrease)	4.95 (0.91-26.0)	0.07
Normal C3 level	4.95 (0.91-26.0)	0.06

Regarding disease activity, there were no meaningful differences in SLEDAI scores between pre-vaccine and post-vaccine visits. Only 11% of patients experienced disease flares after vaccination, 1% of them severe. "The data from our group and others has shown that overall disease activity did not change after vaccination. Our study also showed that severe flares were rare. Most flares were mild to moderate and manageable," Dr Izmirly commented. A limitation of this study is that vaccine efficacy threshold levels are not yet established.

Certain medications or combinations of medications could affect the efficacy of the vaccines. While minimal protective levels remain unknown, these data suggest protocol development is needed to assess the efficacy of booster vaccination. The rare occurrence of severe flares supports the relative safety of vaccination in SLE patients.

1. Izmirly PM, et al. Evaluation of Immune Response and Disease Status in SLE Patients Following SARS

Late-Breaking Posters

Promising results in uric acid-lowering in gout patients with a new xanthine oxidase inhibitor

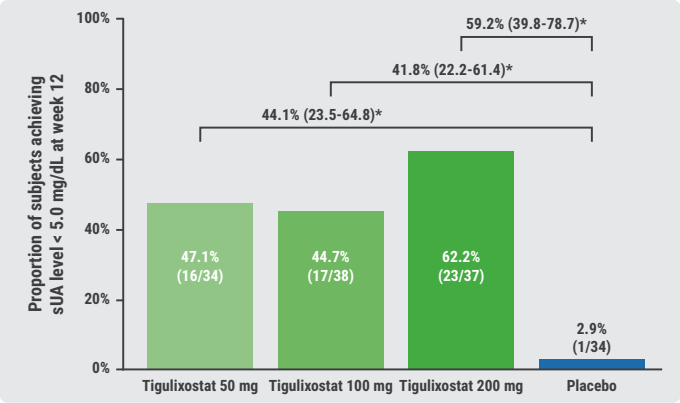
Demonstrating efficacious serum urate-lowering in gout patients with hyperuricemia, tigulixostat is now predestined for further development. No particular safety signals were reported and overall drug tolerance was good in new phase 2 results.

In the effective management of gout, keeping the level of serum uric acid below its limit of solubility is key, but a substantial part of patients does not reach this therapeutic goal [1,2]. "Tigulixostat is a novel selective xanthine oxidase inhibitor and, unlike allopurinol, it does not have a purine-like backbone structure," Prof. Robert Terkeltaub (University of California San Diego, CA, USA) described the new agent.

A phase 2 study (NCT03934099) investigated tigulixostat for safety and efficacy in patients with gout and hyperuricemia [1]. The study population consisted of 156 patients with gout, who were randomised to receive either placebo or tigulixostat at dosages of 50 mg, 100 mg, or 200 mg daily over 12 weeks. After that, an additional 2-week safety follow-up was performed. Participants had to have a serum urate level of >6.0 mg/dL if on prior urate-lowering treatment and a value between 8.0 mg/dL and 12 mg/dL after a washout period, or if previously untreated. Colchicine 0.6 mg was given as gout flare prophylaxis. "The primary endpoint was the proportion of subjects achieving serum urates less than 5.0 mg/dL at week 12, as this target is recommended for severe disease including tophaceous gout," stated Prof. Terkeltaub. The baseline characteristics of the study population included a mean age between 52.0 and 56.6 years, predominantly men, and a mean BMI little above 30 kg/m^2. Prof. Terkeltaub also pointed out that about 20% had palpable tophi, and most pre-dosing serum urate levels were <9.8 mg/dL.

At week 12, 47.1% (50 mg), 44.7% (100 mg), and 62.2% (200 mg) of those on the study drug achieved a serum urate <5.0 mg/dL compared with 2.9% on placebo (P<0.0001 for all dosages; see Figure). The rate of patients reaching the secondary endpoint of serum urate <6.0 mg/dL was also significantly higher when on the study drug, with corresponding proportions of 58.8%, 63.2%, and 78.4% versus 2.9%, respectively. In a small active control group of 13 patients receiving febuxostat, 23% reached serum urate values <5.0 mg/dL.

Figure: Rates of study participants who reached the primary endpoint of a serum uric acid level (sUA) <5 mg/dL at week 12 [1]



*Difference in proportion (%) to placebo with P<0.0001; asymptotic limits of 95% CI and risk difference were determined by the Wald method.

As for safety, 50–56.8% on tigulixostat and 50% on placebo were affected by treatment-emergent adverse events, the majority of mild-to-moderate severity; 4 patients discontinued the study due to adverse events. Between 10.8% and 13.2% of tigulixostat patients and 9.4% of placebo patients experienced a gout flare that required rescue treatment.

"In conclusion, tigulixostat significantly lowered serum urate in gout patients, impressively achieved urate targets, and was well tolerated collectively. These results support its continued development for gout with uncontrolled hyperuricemia," Prof. Terkeltaub summarised.

1. Terkeltaub R. Phase 2 study results from a randomised, double-blind, placebo-controlled, dose-finding study to evaluate efficacy and safety of tigulixostat, a novel non-purine selective xanthine oxidase inhibitor in gout patients with hyperuricemia. Abstract L05, ACR Convergence 2021, 3–10 November.
2. Mu Z, et al. Clin Rheumatol. 2019 Dec;38(12):3511-3519.

Laboratory and clinical signs 24h after hospitalisation predict MIS-C in children

Hypotension, abdominal pain, rash, and serum sodium concentration in children in the first 24 hours after hospital admission were indicators of COVID-19-associated multi-system inflammatory syndrome (MIS-C), according to a retrospective chart review analysis. Identifying affected children early is key to the successful management of this dangerous syndrome.

MIS-C is a new syndrome associated with SARS-CoV-2 infection that has been increasingly reported in children.

Patients with MIS-C usually present with persistent fever, abdominal pain, vomiting, diarrhoea, skin rash, and mucocutaneous lesions. MIS-C associated with COVID-19 may rapidly progress to hypotension and shock with cardiac and other end-organ injuries. "Clinically, we often found it difficult to separate MIS-C from other common childhood illnesses. To solve this problem, we set out to identify features that are distinctive of our patients with MIS-C and to use those for a prediction model," said Dr Matthew Clark (Vanderbilt University Medical Center, TN, USA) [1].

In a retrospective chart review of children admitted to Vanderbilt Children´s Hospital between 10 June 2020 and 8 April 2021 and evaluated for MIS-C, the researchers collected standardised clinical and laboratory features within the first 24 hours of presentation in the hospital. The diagnosis of MIS-C was determined by the treatment team service and retrospectively reviewed and confirmed by both a paediatric rheumatologist and a paediatric infectious disease physician. Logistic regression with bootstrapped backward selection was used to identify the most important predictors for MIS-C.

During the study period, 127 children were admitted for evaluation for MIS-C. In 45 patients, the MIS-C diagnosis was confirmed. In the final risk prediction model, researchers identified 4 predictors for MIS-C: hypotension, abdominal pain, a rash of any kind, and hyponatremia. The model showed excellent discrimination with a C-index of 0.90 (95% CI 0.85–0.94).

The authors demonstrated that their clinical diagnostic prediction model has excellent discrimination and could assist clinicians in distinguishing patients with MIS-C from those without. "We are planning to test our model with external and prospective validation, and hopefully, it can be of use for clinicians in the future," Dr Clark concluded.

1. Clark M, et al. A prediction model to distinguish patients with multisystem inflammatory syndrome in children. Abstract L09, ACR Convergence 2021, 3–10 November.