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PEER-REVIEWED CONFERENCE REPORT

Late-Breaking News
The new anti-GM-CSF receptor alpha monoclonal antibody mavrilimumab could be an interesting novel option for patients with giant cell arteritis.

read more on PAGE 3

COVID-19 and Rheumatic Disease
Poor disease control and therapy with systemic corticosteroids in patients with rheumatic disease are risk factors for more severe COVID-19 disease.

read more on PAGE 8

Lupus Nephritis
Current biomarkers in lupus nephritis have disappointed in the prediction of flares. An "omic"-driven approach might be a successful way for the future.

read more on PAGE 10

MEDICOM MEDICAL PUBLISHERS

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Contents

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Late-Breaking News

Gout treatment with febuxostat: no higher cardiovascular mortality

A new evaluation of the risk for cardiovascular safety under treatment with febuxostat within a post-licensing study demonstrated no higher rates of cardiovascular mortality and major cardiovascular events when compared to allopurinol.

The current post-authorisation study was initiated as suggested by the EMA to obtain data about the cardiovascular (CV) safety of febuxostat in comparison to allopurinol, 2 possible treatments for hyperuricaemia [1]. Previously, the CARES trial (NCT01101035) had raised concerns regarding CV risk with febuxostat that led to changes in treatment recommendations [1,2]. However, given that CV disease risk factors are common in patients with gout, lingering doubts about ascribing such a CV risk to febuxostat persisted.

The FAST trial (ISRCTN72443728) is a multinational, prospective, randomised, parallel group, open-label, non-inferiority, blinded endpoint study [1]. Included were 6,128 adults aged >60 years with an ongoing treatment of allopurinol for gout, who also had ≥1 additional CV risk factor. After patients had been treated to a target urate level of <0.357 mmol/L (<6 mg/dL), they were randomly assigned to continue allopurinol at their necessary dose, or start 80 mg febuxostat per day with increasing dosage to 120 mg daily to meet target uric acid level, after allowing for a washout period for allopurinol of 1-3 weeks.

The primary endpoint was based on a composite of major cardiac events: hospitalisation for non-fatal stroke, non-fatal myocardial infarction or biomarker-positive acute coronary syndrome, or CV death. To determine non-inferiority with a cut-off HR of 1.3, a Cox model was used for an on-treatment (OT) analysis as well as for the intention-to-treat (ITT) population.

Most participants (85.3%) were male. Their baseline mean age was 71 and 33.4% had previously been diagnosed with CV disease. Randomisation was performed 1:1, median follow-up time was 4 years in the study and 3.6 years on treatment. As for events, febuxostat was non-inferior to allopurinol with significant differences in both the OT and ITT analyses (P<0.001). The OT result for all-cause mortality was nominally lower for febuxostat with an HR of 0.75 (95% CI 0.59–0.95), but not significant in the ITT analysis: HR 0.84 (95% CI 0.71–1.01). Both analyses for CV death also demonstrated insufficient evidence to conclude that the groups were statistically significantly different.

Regarding serious adverse events (SAEs), there were 222 (7.2%) deaths in the febuxostat and 263 (8.6%) in the allopurinol group and 59.4% of the allopurinol recipients experienced at least 1 SAE versus 57.3% treated with febuxostat.

In summary, febuxostat was determined non-inferior to allopurinol in both the OT and ITT analyses. "In contrast to previous studies, there was no evidence of increased mortality with febuxostat and we believe that regulators should review febuxostat licensing restrictions," Prof. Thomas MacDonald (University of Dundee, UK) concluded his talk.

1 MacDonald T, et al. Long term cardiovascular safety of febuxostat and allopurinol in patients with chronic gout: the febuxostat versus allopurinol streamlined trial, L08, ACR Convergence 2020, 5-9 Nov.
2 White WB, et al. N Engl J Med. 2018;378:1200-10.

New agent with great potential for the treatment of giant cell arteritis in the pipeline

Lower risk of flare and increased sustained remission with mavrilimumab compared with placebo were the main results of a trial for giant cell arteritis with the novel anti-GM-CSF receptor alpha monoclonal antibody.

"A substantial proportion of patients treated with tocilizumab fail treatment due to relapse or tocilizumab-related side effects. IL-6 blockade may primarily target the Th17 axis, possibly leaving significant residual Th1 activity," Dr Maria Cinta Cid (Hospital Clínic of Barcelona, Spain) described the current situation in the treatment of giant cell arteritis (GCA). She observed a great unmet need for new treatments in GCA [1].

Dr Cid presented a phase 2, randomised, placebo-controlled study investigating mavrilimumab in patients with new-

onset (N/O) or relapsing refractory (R/R) GCA. All patients had to be in corticosteroid-induced remission when starting the trial, meaning: no clinical symptoms, C-reactive protein (CRP) <1 mg/dL and erythrocyte sedimentation rate (ESR) <20 mm/h. Prednisone was tapered according to a pre-determined protocol over the 26-week study duration. In the double-blind treatment period, patients were either treated with mavrilimumab 150 mg (n=42) or placebo (n=28) subcutaneously every 2 weeks. The time to the incidence of the first GCA flare by week 26 was defined as the primary endpoint. A flare was defined as having ESR ≥30 mm/h and/or CRP ≥1 mg/dL elevation plus ≥1 new cranial or extracranial GCA manifestations, or new/worsening vasculitis detected by imaging. The key secondary endpoint was defined as the percentage of patients with sustained remission at week 26.

Baseline patient features included a mean age of 69.7 and 71% of patients were female. The study population consisted of 35 N/O patients and 35 R/R patients. "Clinical manifestations were predominantly cranial," said Dr Cid. She further indicated that nearly 3 quarters of diagnosis confirmation by ultrasound in the study population could reflect a shift in standard-of-care.

At week 26, GCA flares were noted in 19% of the mavrilimumab patients as opposed to 46.4% of the placebo group. The median time to flare by week 26 was 25.1 weeks in the placebo group. Time to flare in the mavrilimumab group was not estimable as the events were too scarce, but when comparing mavrilimumab with placebo, there was a significantly lower hazard with mavrilimumab treatment (HR 0.38). This corresponded to a 62% reduction in risk of flare for mavrilimumab recipients (P=0.026). Also, significantly higher rates of sustained remission were observed for mavrilimumab recipients (83.2%) compared with those receiving placebo (49.9%; P=0.0038).

Mavrilimumab was overall well tolerated and adverse events were mostly mild to moderate with a comparable distribution among the groups. Importantly, no cases of death or loss of vision happened. Out of 5 serious adverse events, 2 were in the mavrilimumab group and 3 in the placebo group, none were deemed to be drug-related. "These results are encouraging for the potential further development of mavrilimumab in GCA," Dr Cid concluded. Thus far, GM-CSF antagonism has been used in trials in RA and is being evaluated in other rheumatology settings and in severe COVID-19 pneumonia. We await to see where targeting of this pathway may enter the clinic.

1. Cid MC, et al. Mavrilimumab reduces time to flare and increases sustained remission in a phase 2 trial of patients with giant cell arteritis. L06, ACR Convergence 2020, 5-9 Nov.

Autotaxin inhibitor successful in the first trial in diffuse cutaneous systemic sclerosis

Autotaxin inhibition is a fascinating novel treatment approach for systemic sclerosis patients, where there are no specific treatment options. Ziritaxestat proved to be efficacious and tolerable in a phase 2 trial.

Vasculopathy, inflammation, and fibrosis form a specific triad of features found in systemic sclerosis (SSc), a disease with a high unmet need for novel treatments. While the pathogenesis of SSc remains uncertain, lysophosphatidic acid (LPA) is a well-known pro-fibrotic and pro-inflammatory lysophospholipid that has been implicated in the pathogenesis of SSc. LPA is generated at sites of inflammation by autotaxin-mediated hydrolysis of lysophosphatidylcholine and other lysophospholipids. Ziritaxestat is an autotaxin inhibitor with a novel mechanism of action that could be promising for modulating the skin pathology of SSc and as such might be able to fill the current treatment gap. The current randomised, double-blind, placebo-controlled phase 2a trial was the first to evaluate oral administration of ziritaxestat in patients with early diffuse cutaneous SSc [1].

Adult patients with diffuse cutaneous SSc (n=33) were randomised 2:1 to receive oral ziritaxestat 600 mg once daily or matching placebo for 24 weeks. Immunosuppressive background therapies were allowed to continue unchanged if doses were stable for ≥3 months prior to ziritaxestat treatment. All patients had a modified Rodnan skin score (mRSS) >10 at screening. The primary endpoint was change from baseline mRSS at 24 weeks. Other endpoints were Health Assessment Questionnaire Disability Index (HAQ-DI) and Combined Response Index for Systemic Sclerosis (ACR CRISS) score. Safety data was collected as well.

The majority of patients in the ziritaxestat (95.2%) and placebo (83.3%) groups were on background immunosuppressive therapy. At baseline, mean (SD) mRSS was 27.0 (8.8) and 22.5 (6.2), respectively. A statistically significant difference was observed between groups for mRSS from week 16 up to week 24: least square mean difference was -2.8 (95% CI

-5.6 to -0.1) for ziritaxestat versus placebo (P=0.0411) at week 24. "This effect is significant because this improvement happened despite the background immunosuppressive therapy," Prof. Dinesh Khanna (University of Michigan Scleroderma Program, USA) explained.

In addition, the ACR CRISS showed likelihood for improvement. Treatment with ziritaxestat did not influence lung function. Target inhibition was reflected by an average reduction in circulating lysophosphatidic acid of about 80%.

Adverse events (AEs) were mild or moderate; no treatment-emergent AE led to study drug discontinuation. Serious treatment-emergent AEs occurred in 2 patients in the ziritaxestat group and 1 patient in the placebo group, all of them were considered unrelated or unlikely to be related to the study drug. "We believe that these results support a possible role for the autotaxin pathway in early dermal SSc," Prof. Khanna concluded. This works represents an interesting concept in SSc whereby cutaneous fibrosis may be modulated independently of systemic fibrosis including lung disease. Much interesting exploratory science could flow from these observations.

1. Khanna D, et al. A Phase 2a Randomized, Double-blind, Placebo-controlled Study of Ziritaxestat in Early Diffuse Cutaneous Systemic Sclerosis (NOVESA). L09, ACR Convergence 2020, 5-9 Nov.

JAK inhibition as a treatment option for ankylosing spondylitis

Tofacitinib demonstrated very promising results for oral treatment of active ankylosing spondylitis in a phase 3 trial. New safety risks were not detected.

Several types of immune cells playing a role in the pathogenesis of spondyloarthritis use JAK pathways [1]. Hence, not surprisingly, JAK inhibitors such as tofacitinib have already shown promising results in phase 2 trials for ankylosing spondylitis (AS) and therefore have potential to become a therapeutic option for this indication in the future [2,3].

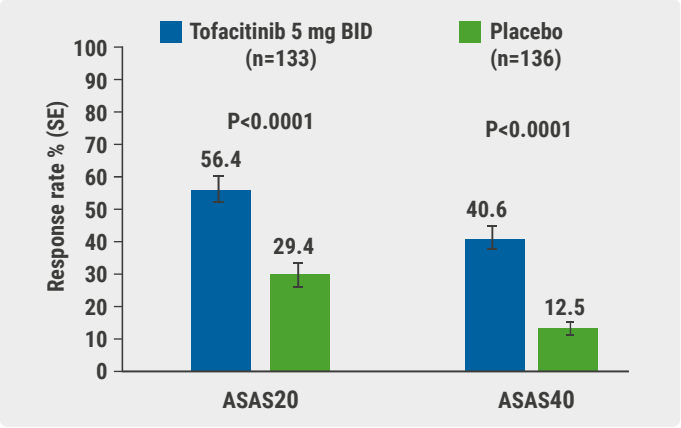
The oral JAK inhibitor tofacitinib is now investigated in phase 3 for the treatment of AS [4]. This randomised, placebo-controlled, double-blind study included 269 adult patients with active AS, who met the modified New York criteria in centrally read radiographs. All patients had inadequate response or were intolerant to treatment with at least 2 non-steroidal anti-inflammatory drugs (NSAIDs). A primary analysis of the still ongoing trial was reported.

Over 16 weeks, study subjects were either treated with twice daily 5 mg tofacitinib or placebo. In the following open-label extension, all patients received 5 mg tofacitinib twice daily until week 48. The primary endpoint was defined as Assessment in Ankylosing Spondylitis (ASAS)20 response at week 16. The key secondary endpoint was ASAS40 achievement. Furthermore, 4 groups of endpoints for efficacy were evaluated at week 16, including change in various outcome types. Safety data was available up to week 48.

Baseline patient characteristics were: 85% males, the average age was 41, symptom duration was ~13 years, Ankylosing Spondylitis Disease Activity Score (ASDAS) was 3.8 for the group receiving tofacitinib and 3.9 for the group receiving placebo. "The majority of patients (80%) were naïve to biologic disease-modifying antirheumatic drugs (DMARDs) and 20% were inadequate responders to TNF inhibitors or had experienced biologic DMARDs in the past," explained Prof. Atul Deodhar (Oregon Health & Science University, USA).

The rate of patients achieving an ASAS20 response at week 16 was 56.4% with tofacitinib and 29.4% with placebo (P<0.0001; see Figure). Furthermore, the percentage of ASAS40-responding patients at week 16 was significantly higher in those treated with tofacitinib (40.6%) than in those receiving placebo (12.5%; P<0.0001). ASDAS was significantly reduced by 1.36 for tofacitinib versus 0.39 for placebo (P<0.001). Comparisons for the ASAS components as well as various other secondary endpoints including CRP reduction were all significant in favour of tofacitinib treatment.

Figure. Tofacitinib in ankylosing spondylitis: primary and key secondary endpoints were achieved [4]



ASAS, Assessment in Ankylosing Spondylitis; BID, twice daily.

Concerning safety up to week 16, adverse events (AEs) were registered for 54.1% in the tofacitinib and 51.5% in the placebo group, with rates for serious AEs of 1.5% and 0%, respectively. Study discontinuation due to AEs at week 16 was low: 2.3% for tofacitinib versus 0.7% for placebo. "There were no unexpected side effects in this study," said Prof. Deodhar. Concerning safety up to week 48, he further elaborated: "There were no malignancies, no thromboembolic events, no major adverse cardiac events, and no gastrointestinal perforations."

In conclusion, the study met its primary and secondary endpoints with the demonstration of significant superiority of tofacitinib over placebo in the treatment of active AS and adds to the body of literature supporting the efficacy of JAK inhibition in AS and the seronegative spondyloarthropathies.

1. Veale DJ, et al. Rheumatology (Oxford). 2019;58:197-205
2. Van der Heijde D, et al. Ann Rheum Dis. 2017;76:1340-7.
3. Poddubnyy D, Sieper J. Curr Rheumatol Rep. 2020;22:47
4. Deodhar A, et al. Tofacitinib for the treatment of adult patients with ankylosing spondylitis: primary analysis of a phase 3, randomized, double-blind, placebo-controlled study. L11, ACR Convergence 2020, 5-9 Nov.

Spotlight on Rheumatoid Arthritis

Persuasive long-term results for JAK inhibition in rheumatoid arthritis

Over 7 years, the oral JAK inhibitor upadacitinib showed convincing results for lasting efficacy in patients with rheumatoid arthritis within the SELECT-MONOTHERAPY trial.

Upadacitinib as monotherapy already demonstrated significant results after 14 weeks in patients with moderate-to-severe rheumatoid arthritis (RA) compared with methotrexate within the SELECT-MONOTHERAPY (NCT02706951) study [1]. The current analysis focused on drug performance over 84 weeks [2].

Within the long-term extension of SELECT-MONOTHERAPY, 598 patients continued their previous medication with upadacitinib 15 or 30 mg or were switched to one of the upadacitinib doses in case of preceding methotrexate therapy, as prespecified at baseline.

"By week 84, approximately 80% of patients in either treatment group, blinded upadacitinib 15 or 30 mg, remained in the study," said Prof. Josef Smolen (Medical University of Vienna, Austria). Baseline characteristics were balanced over the different treatment groups. They comprised 81% females, a mean of 6.6 ± 7.58 years since RA diagnosis, mean Disease Activity Score (DAS)28 using C-reactive protein (CRP) was 5.6 ± 1.0, mean clinical disease activity index (CDAI) was 38.0. In total, exposure to upadacitinib 15 mg corresponded to 421.5 patient-years (PY) and upadacitinib 30 mg to 425.9 PY.

Treatment-emerging adverse events occurred in the upadacitinib groups at a rate of ≥5/100 PY and were most frequently seen as urinary tract infections, creatine phosphokinase (CPK) elevation, or upper respiratory tract infections. "Events of herpes zoster infections, hepatic disorders, and CPK elevation were higher among patients receiving upadacitinib 30 mg, while rates of serious infections and malignancy appeared comparable between the doses," revealed Prof. Smolen regarding long-term safety. He pointed out that the most common serious adverse event was pneumonia, occurring at 1.7 events/100 PY in the upadacitinib 15 mg group and 0.7 events/100 PY in the upadacitinib 30 mg group.

Concerning efficacy, 71% (upadacitinib 15 mg) and 78% (upadacitinib 30 mg) reached American College of Rheumatology (ACR)50 responses at week 84. The respective rates for DAS28 <2.6 were 60% and 77%, respectively. CDAI ≤10 was attained by 55% (upadacitinib 15 mg) and 67% (upadacitinib 30 mg). "Approximately one-quarter to one-third of patients receiving upadacitinib achieved CDAI and ACR/EULAR-based Boolean definitions of remission at week 84," said Prof. Smolen. Furthermore, reductions in pain and physical function were also maintained until week 84.

"In summary, upadacitinib monotherapy resulted in continued and sustained benefit through 84 weeks with no new safety signals identified," concluded Prof. Smolen.

1. Smolen JS, et al. Lancet. 2019;393:2303-11.
2. Smolen JS, et al. Upadacitinib as monotherapy in patients with rheumatoid arthritis and prior inadequate response to methotrexate: results at 84 weeks. P0209, ACR Convergence 2020, 5-9 Nov.

Rheumatoid arthritis: new EULAR treatment guidelines

Several new developments have led to changes in the EULAR recommendations to treat rheumatoid arthritis. They include the use of JAK inhibitors, short-term corticosteroid administration, and treatment tapering.

The new EULAR guidelines on the management of rheumatoid arthritis (RA) were presented by Prof. Daniel Aletaha (Medical University Vienna, Austria) [1,2]. His presentation covered the following topics: treat-to-target and remission, precision medicine, expanding therapeutic opportunities, glucocorticoids, and possible treatment reduction decisions [1].

The treat-to-target approach has been widely implemented among rheumatologists for about 10 years. Remission criteria are not new, but recently, there has been some discussion on the role of Patient Global Assessment (PGA) within the Boolean criteria. There is ongoing research about the use of increasing the cut-off point for the PGA to improve the consistency of the Boolean criteria with the Simple Disease Activity Index (SDAI) criteria.

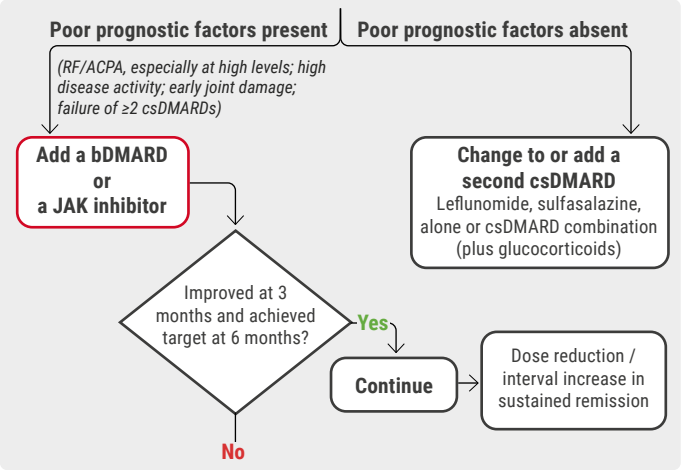
Regarding precision medicine, Prof. Aletaha indicated that, currently, there are no single or combined markers that drive treatment guidance for RA patients at baseline to tailor biologic treatment. "The problem is that often only one therapy is investigated based on clinical trials that are analysed. Often we only look at "-omics" and we should be thinking about a broader context, maybe going to socio-demographics and age, or other factors that –combined with biological data– can create a biotype that can then be used to try and predict a phenotype. These markers will then give you the precision-medicine approach," Prof. Aletaha elaborated. Hence, the challenges of precision medicine might be partly due to the heterogeneity of outcome and the lack of phenotypes of response.

JAK Inhibitors: a novel addition in the guidelines

The EULAR recommendations newly implemented JAK inhibitors on the same level as biologic DMARDs after failure of methotrexate (see Figure). Concerning small molecules, Prof. Aletaha recapitulated that the targeted synthetics approach various targets while biologics are highly efficient for one specific target and may indirectly target others.

As for glucocorticoids: they should be combined short term with conventional DMARDs. This is partly based on outcomes from the IDEA study [3]. In IDEA, methotrexate plus infliximab had no statistically significant superiority over methotrexate plus high-dose corticosteroids in DMARD-naïve early RA patients. Furthermore, the NORD-STAR trial (NCT01491815) assessed aggressive conventional therapy including corticosteroids and the results showed that it had relative non-inferiority compared with other treatments like biologics [4].

Figure. New position of JAK inhibition in the EULAR 2020 recommendations [2]



RF, rheumatoid factor; ACPA, anticitrullinated protein antibody; DMARDs, disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic DMARDs; bDMARD, biologic DMARD.

The last subject covered was medication tapering for patients who reached their treatment target recommended by the current EULAR algorithm [1]. "The most important question when we want to taper off patients on biological DMARDs is: which predictors are indicating successful discontinuation," said Prof. Aletaha. He indicated that these include low disease activity, better physical function, absence or low presence of rheumatoid factor (RF) or anticitrullinated protein antibody (ACPA), low levels of C-reactive protein (CRP), shorter disease duration, and low signals of disease activity by ultrasound.

1. Aletaha D. In 2020, what recent data guide treatment decisions in rheumatoid arthritis? 4S005, ACR Convergence 2020, 5-9 Nov.
2. Smolen JS, et al. Ann Rheum Dis. 2020;79:685-99.
3. Nam JL, et al. Ann Rheum Dis. 2014;73:75-85.
4. Hetland ML, et al. L09, 2019 ACR/ARP Annual Meeting.

Rheumatoid arthritis and interstitial lung disease: a deadly combination

Rheumatoid arthritis-associated interstitial lung disease is difficult to control. The combination of DMARDs with antifibrotics might improve the prognosis for this difficult-to-treat patient population.

"Approximately 25% of patients with rheumatoid arthritis (RA)-associated interstitial lung disease (ILD) die in the first year after diagnosis, and only around 20% are alive 8 years after the initial diagnosis," Prof. Joan Bathon (Columbia University, USA) said [1]. Thus, mortality is considerably higher compared with RA patients without ILD. In total, the prevalence of RA-associated ILD is estimated between 8% and 15%, a 9-fold risk elevation compared to the general population.

How RA medications influence the risk of developing ILD is a matter of debate. "It seems unlikely that methotrexate is worsening ILD, but I don´t know whether we will ever get to the root of this problem because RA itself is causing ILD and sorting this out from the treatment is always difficult," Prof. Bathon said.

Concerning a DMARD that may treat both ILD and arthritis, there is only scarce data for targeted DMARDs. There are open-label studies regarding B-cell depletion therapy with rituximab and T-cell co-stimulatory inhibitor therapy with abatacept that suggested disease stabilisation, for example. There is data on the IL-6 receptor blocker tocilizumab only in systemic sclerosis, not in RA-ILD. In systemic sclerosis, a slower decline in pulmonary function tests was observed in the tocilizumab group versus placebo, "so there might be some hope that an improvement might also be the case in RA," Prof. Bathon said.

The antifibrotics nintedanib and pirfenidone are approved for idiopathic pulmonary fibrosis (IPF). The tyrosine kinase inhibitor nintedanib was also tested in patients with autoimmune disease, namely in patients with systemic sclerosis-associated ILD in the SENSCIS trial. In this study, lung function decline was reduced by about 50% in the nintedanib arm compared with the placebo group. In the INBUILD trial, nintedanib was assessed in fibrosing ILDs other than IPF: 25% of patients suffered from autoimmune ILDs, including RA. The agent slowed down lung function deterioration by 57%. "The efficacy was similar among all autoimmune ILDs. This is very encouraging because some of these patients had RA," Prof. Bathon concluded. At present, there is no data on pirfenidone on RA-ILD, but there is a trial in progress now.

Furthermore, another question is whether it is safe to combine nintedanib or pirfenidone with a conventional DMARD and/or a targeted DMARD. "Probably. We need more data for this answer, but at least for nintedanib, we have some data from the INBUILD trial, where patients with RA were allowed to remain on DMARDs. There was no report on synergistic or added toxicity," concluded Prof. Bathon.

1 Bathon J. RA & Interstitial Lung Disease. 3S010, ACR Convergence 2020, 5-9 Nov.

COVID-19 – What Rheumatologists Need to Know

COVID-19 in patients with rheumatic disease: most report mild disease

A new study presented during the ACR Convergence 2020 demonstrated that patients with rheumatic disease have a low incidence of COVID-19 with most patients having a mild disease course.

"When the pandemic started, there was concern on whether to continue or hold immune therapies among patients with rheumatic diseases because they are at increased risk for infection," says the study's co-author, Dr Akhil Sood (University of Texas Medical Branch, USA) [1]. To explore the risk for SARS-CoV-2 infection and outcomes in patients with rheumatic disease, the researchers performed a systematic literature search in PubMed/Medline and Scopus to identify relevant studies from January to June 2020 that reported the outcomes of COVID-19 among these patients.

The final review included 6,095 patients with rheumatic diseases from 8 observational cohort studies, with 28% having rheumatoid arthritis (RA) and 7% having psoriatic arthritis (PsA). Of the 6,095 patients, 123 (2%) tested positive or had a high clinical suspicion for COVID-19. Across all the studies used for the review, 68% of COVID-19 patients were taking biologics, with 31% taking anti-TNF drugs and 6% JAK inhibitors. Among patients infected with SARS-CoV-2, 91 (73%) were never hospitalised. 13 patients who were hospitalised required admission to an intensive care unit and 4 patients died. "The incidence of COVID-19 among patients with rheumatic disease was low," Dr Sood concluded. "In our analysis, there was a small number of patients on biologics and targeted therapies to make definite conclusions on whether to continue or hold therapies," said Dr Sood. Therefore, larger cohort studies are necessary to examine the outcomes of COVID-19 among biologic and non-biologic users. Finally, we must consider that rheumatology patients on DMARDs, especially higher-risk cases with cardiovascular and pulmonary disease, may have been shielding during the pandemic.

1 Sood A, et al. COVID-19 infection among patients with rheumatic disease on biologic & targeted therapies: a systematic review. P0008, ACR Convergence 2020, 5-9 Nov.

Poor disease control: a risk factor for severe COVID-19

Data from the COVID-19 Global Rheumatology Alliance Registry showed that high disease activity is a risk factor for poor outcomes from COVID-19.

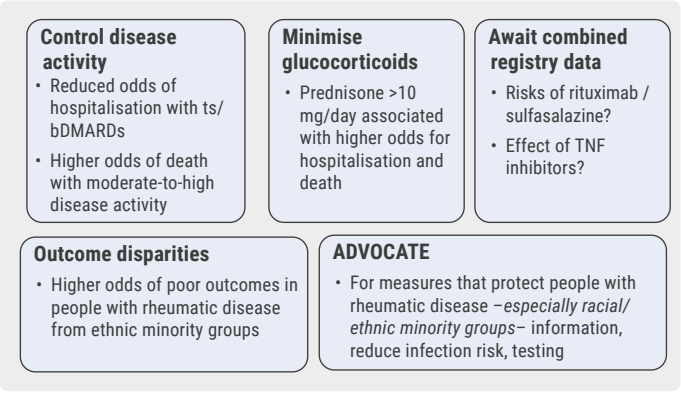
"Our registry is a global initiative where cases from Europe are entered by the EULAR and cases in the USA by the ACR," Prof. Rebecca Grainger (University of Otago, New Zealand) explained [1].

Three analyses were presented during the meeting. The risk of hospitalisation was assessed after the first month of the registry in the European and US cohort, risk factors for death in July in the American cohort, and outcome disparities in the global cohort that included data until August. In the first analysis, 600 cases were included: 277 were hospitalised (46%), 55 died (9%). Most patients suffered from rheumatoid arthritis (RA; 38%) and comorbidities were common. Patients aged >65 years had a 2.55-fold increased risk of hospitalisation. The hospitalisation risk of patients that were treated with a prednisone-equivalent of over 10 mg/day was 2.1-fold elevated. Comorbidity of different organ systems was associated with an up to 3-fold elevated risk of hospitalisation. "It is worth noting that the pre-COVID-19 use of DMARDs or biologics was associated with a reduced risk of hospitalisation," Prof. Grainger said.

In the second analysis, risk factors for death due to a SARS-CoV-2 infection were analysed in 1,324 US cases. In this analysis, Black, Asian American, and Latinx patients had a higher risk of hospitalisation, whereas there was no difference in mortality. Latinx patients had a more than 3-fold elevated risk for ventilatory support.

In the largest analysis, a total of 3,729 patients (two-third from Europe and one-third from the USA) were included. The risk of death from COVID-19 was associated with age, male gender, ever smokers, but the latter only in RA patients, and moderate-to-severe disease activity. COVID-19 fatalities were associated with no DMARD use, both sulfasalazine and rituximab treatment, and therapy with glucocorticoids >10 mg per day. As Prof. Grainger explained, these data reveal some learning points (see Figure). "First, it is important to control disease activity as reduced odds of hospitalisation were seen in patients treated with biologic and targeted systemic DMARDs in analysis 1 and there were higher odds of death in patients with moderate-to-high disease activity in analysis 3," Prof. Grainer said. Second, therapy with glucocorticoids should be minimised and possibly be <10 mg/day, as higher doses are associated with an increased risk for hospitalisation and death. Due to worse outcome in ethnic minority groups, one should advocate measures to protect these people.

Figure. 5 learning points from International COVID-19 Registries [1]



ts, targeted systemic; b, biologic.

1. Grainger R, Lessons from the COVID-19 Global Rheumatology Registry: Epidemiology, Risk Factors & Outcomes. ACR Convergence 2020, 5-9 Nov.

No heightened outcome risk for rheumatic patients with COVID-19

When infected with SARS-CoV-2, the risk for a severe disease course including mechanical ventilation was not higher for patients with rheumatoid comorbidity compared to the general population.

"Early in the pandemic we observed a higher risk of mechanical ventilation in patients with rheumatic diseases compared with the general population in a small cohort study," stated Dr Naomi Serling-Boyd (Massachusetts General Hospital, USA) [1]. However, the situation is still not entirely clear [2]. "Therefore, we conducted a comparative cohort study of patients with COVID-19 as confirmed by PCR between January and July 2020 in our multicentre healthcare system," she further explained.

Out of 12,866 COVID-19 cases during this period, 143 patients already diagnosed with rheumatic disease (RMD) were matched by age, sex, and date of COVID-19 PCR with up to 5 comparators without RMD (n=688). Within the RMD group, mean age was 60 years, 76% were female, 52% never-smokers, and the median Charlson comorbidity index (CCI) equalled 2. In the non-RMD group mean age was 59, 76% were female, 50% never-smokers, and CCI equalled 0. The most common rheumatic diagnoses were rheumatoid arthritis (31%) and systemic lupus erythematosus (19%). The rheumatic patients had ongoing treatments with corticosteroids (36%), hydroxychloroquine (21%), conventional synthetic DMARDs (31%), and biologic DMARDs (29%).

No disparities in risk for intensive care, hospital admission, or death were found between the groups. The unadjusted results of a Cox proportional hazard model pointed to a higher risk only for mechanical ventilation with an HR of 1.75 (95% CI 1.12–2.74). Nonetheless, after adjustment for race, smoking, and CCI, this increased risk was no longer significant (HR 1.51; 95% CI 0.93–2.44). Hence, RMD and non-RMD patients had a similar outcome risk for COVID-19. "These findings provide reassurance for RMD patients, though close monitoring of patients with other comorbidities is warranted," Dr Serling-Boyd closed her talk. As the world is in the throws of the second peak of the COVID-19 pandemic, the overall data presented in relationship to RMD and, more importantly, immunosuppressive therapy is very reassuring. Indeed, more than one class of rheumatic drug has evidence for efficacy in severe COVID-19.

1 D'Silva KM, et al. Ann Rheum Dis. 2020;79:1156-62.
2 Serling-Boyd N, et al. Outcomes of COVID-19 infection in patients with rheumatic diseases in a multicenter healthcare system: a comparative cohort study. L01, ACR Convergence 2020, 5-9 Nov.

What Is Hot in Lupus Nephritis?

Lupus nephritis biomarkers: moving toward an omic-driven approach

Lupus nephritis affects up to 60% of patients with systemic lupus erythematosus. Current biomarkers are not reliable, but a novel "omic"-driven approach might be a more successful way for risk prediction.

"In lupus nephritis, we believe that 'time is kidney'," said Prof. Chaim Putterman (Albert Einstein College of Medicine, USA) [1]. Lupus nephritis (LN) is a major risk factor for morbidity and mortality in systemic lupus erythematosus (SLE). According to a study, delay between the detection of the onset of renal disease and renal biopsy was a significant predictor for subsequent renal insufficiency and death due to lupus renal involvement. Therefore, biomarkers are of particular importance in LN, because early diagnosis and treatment make a difference. Prompt therapy with prednisone and immunosuppressive agents in LN has a beneficial effect on long-term prognosis.

Unfortunately, increasing double-stranded (ds)DNA antibodies, presently used as biomarkers, were predictive of flares in some, but not all, studies. Therefore, more reliable flare predictors are urgently needed. There is a need for better biomarkers for differentiating lupus versus other diseases, measuring disease activity, predicting outcomes/response to therapy, allowing assessment of response to therapy, and predicting long-term prognosis.

Promising agents are cell-bound complement activation products (CB-CAPs). Studies have shown that CB-CAPs can be helpful in the diagnosis of lupus and are more reliable than anti-dsDNA. Abnormalities in CB-CAPs are associated with higher disease severity in lupus patients.

"Terminal complement activation has also been assessed as a possible biomarker in LN. Tubular C9-positive staining was observed in 23% of biopsies of patients with LN and those patients had significantly higher proteinuria, interstitial fibrosis, and chronicity indices," Prof. Putterman explained.

Big data are the new kid on the block, namely "omics"-driven research instead of hypothesis-driven research. In this approach, instead of a single marker, rather all molecules are assessed, so in more breadth than depth. "Instead of focusing on an individual molecule, we are profiling many analytes simultaneously. If you look at 5, 6, or 7 markers at a time, those perform much better than just a single mediator," Prof. Putterman stated. In one study, 1,000 proteins in the urine of SLE patients were assessed using a quantitative planar protein microarray. In this study, the proteins angptl4, L-selectin, and TGF-β1 were associated with disease activity and were best at tracking concurrent or pending disease flares.
Concerning LN, urine proteins that best distinguish active LN from inactive disease are ALCAM, VCAM-1, Hemopexin, and TFP-1. The CD6-ALCAM pathway is an important driver of inflammation in LN and may also be an interesting target for drug development. Itolizumab is the first antibody that binds to CD6 and decreases pro-inflammatory cytokine secretion. It is now entering a phase-1 trial.

However, anti-dsDNA antibodies and complement components are still the best markers for early diagnosis of LN available today. "My prediction is that the goals of precision medicine in SLE will be realised through big data approaches, rather than tests on single mediators," Prof. Putterman concluded.

1. Putterman C. New biomarkers in lupus nephritis. 4S060, ACR Convergence 2020, 5-9 Nov.

Lupus nephritis: new therapies on the horizon in 2020

Lupus nephritis is a major risk factor for morbidity and mortality in systemic lupus erythematosus. Three novel agents might have the potential to improve therapy in the future.

Both the European and US guidelines for the management of lupus nephritis (LN) are almost 9 years old [1,2]. They propose mycophenolate mofetil (MMF) or cyclophosphamide as first-line agents with the addition of glucocorticoids for optimal responses. Second-line agents include rituximab or calcineurin inhibitors. Naturally, these current guidelines are mainly based on clinical evidence and do not account for new perceptions of pathology and the latest studies.

Therefore, Prof. Joan T. Merrill (Oklahoma Medical Research Foundation, USA) covered the new therapies in the drug pipeline in 2020 for LN [3]. The first candidate is the anti-CD20 monoclonal antibody obinutuzumab that was evaluated as add-on treatment to MMF versus placebo plus MMF in a phase 2 trial. To get a better understanding of the efficacy of obinutuzumab, corticosteroids were rapidly tapered. The overall response rates in the obinutuzumab group reached 55.6%, statistically significantly superior to the placebo group (35.5%; P=0.0246). Adverse events were similar among the groups.

Another interesting agent is the B-cell activating factor (BAFF) inhibitor belimumab. In a phase 3 trial, belimumab was added to standard-of-care. This led to a significantly higher chance of achieving a partial and complete response, which was maintained through week 104 compared with placebo (P=0.002 for both comparisons).

Another interesting agent is the calcineurin inhibitor voclosporin, which has an improved safety profile compared with other calcineurin inhibitors. This small modification results in less pharmacokinetic and pharmacodynamic variability. The substance was created by making a small structural change to cyclosporine. Previously, voclosporin was assessed within the AURA phase 2b trial which included 265 patients, all of whom were on a baseline medication of MMF and steroids. In AURA, 32.6% of patients on twice daily (BID) 23.7 mg of voclosporin achieved complete remission as well as 27.3% on 39.5 mg BID versus 19.3% on placebo. This trial also tapered steroids fast to better recognise the treatment effect of voclosporin. Unfortunately, safety data raised some concerns, because the dosing group treated with 23.7 mg BID had far more serious adverse events.

This year, a phase 3 voclosporin trial met its primary endpoint of renal response at week 52: this was seen in 40.8% of patients receiving voclosporin (23.7 mg BID) plus MMF (1 g BID) and a rapid steroid taper compared with 22.5% of those given MMF and tapered steroids alone (P<0.001) [4]. In this trial, the safety profile was similar in the 2 arms, with serious adverse events being reported in 20.8% of the voclosporin group and 21.3% of the control group. Serious infections were seen in 10.1% of the voclosporin group and 11.2% of controls. Hence, the future looks brighter for the management of LN.

1 Bertsias GK, et al. Ann Rheum Dis 2012:71:1771-82.
2 Hahn BH, et al. Arthritis Care Res 2012;64:797-808.
3 Merrill JT, et al. New therapies for LN in 2020. 4S060, ACR Convergence 2020, 5-9 Nov.
4 Arriens C, et al. Abstract OP0277, EULAR 2020 eCongress, 3-6 June.

Spondyloarthritis – The Beat Goes On

Signs of benefit for T2T in axial spondyloarthritis

Although a treat-to-target strategy for managing patients with axial spondyloarthritis failed to meet its primary efficacy endpoint, there were several signs of benefit in the secondary outcomes compared with standard-of-care in the TICOSPA trial.

The treat-to-target (T2T) management strategy is already adopted in rheumatoid arthritis (RA) patients and also recommended for axial spondylarthritis (axSpA), but no study has evaluated its benefit. The TICOSPA study (NCT03043846) aimed to assess whether patients with axSpA benefit from this approach [1]. The trial was performed at 10 French centres and 4 centres each in Belgium and the Netherlands. Included patients had an Ankylosing Spondylitis Disease Activity Score (ASDAS) >2.1 and had not yet received a biologic. Patients (n=160) were randomised 1:1 to either T2T or standard-of-care. Patients in the T2T group attended consultations every 4 weeks rather than every 3 months with standard-of-care and required a pre-defined management strategy aiming at a target (ASDAS <2.1).

The primary efficacy endpoint was an improvement of at least 30% in the Assessment of Spondyloarthritis International Society Health Index (ASAS HI), a measure of health-related quality-of-life. After 12 months, the 80 axSpA patients assigned to the T2T regimen had a 47% rate of attainment of the primary endpoint, compared with 36% of the patients assigned to standard-of-care, an 11% absolute between-group difference that, nonetheless, failed to achieve statistical significance. However, 6 secondary outcomes showed statistically significant improvements compared with the control patients, including the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score and the ASAS20 and ASAS40 response rates.

Interestingly, a cost-efficacy analysis demonstrated the superiority of T2T over standard-of-care: better outcomes were produced with lower total costs although twice as many patients on T2T strategy received a biologic compared with patients in the standard-of-care group. "Statistical significance was not achieved for the primary efficacy endpoint, but a general trend in favour of T2T was observed in other outcomes with a similar safety profile," concluded Dr Anna Moltó (Cochin Hospital, France). In T2T strategies in RA, the target –joint synovitis– is visible, so the clinician can see what they are aiming for. In SpA, however, the target of inflammation is invisible and hidden in the spinal column, which renders the T2T strategy more challenging. Therefore, the challenge is more difficult but progress is being made.

1. Moltó A, et al. Cluster-randomized pragmatic clinical trial evaluating the potential benefit of a tight-control and treat-to-target strategy in axial spondyloarthritis: the results of the TICOSPA trial. 1444, ACR Convergence 2020, 5-9 Nov.

Artificial intelligence can help in the diagnosis of axSPA

In a study, an artificial neural network was remarkably successful in the assessment of radiographic sacroiliitis.

The reliability of radiographic sacroiliitis assessment is known to be poor. Expert readers –as opposed to evaluation by local rheumatologists or radiologists– usually produce more reliable results, but they are not available in many locations. "We see a big discrepancy between the local and central assessment of sacroiliitis reaching sometimes half of the cases," Prof. Denis Poddubnyy (Charité Universitätsmedizin Berlin, Germany) said. Can artificial intelligence support the diagnosis?

For this study, Prof. Poddubnyy and his team used conventional radiographs of sacroiliac joints from 2 independent cohorts of patients with axial spondylarthritis (axSpa), including 1,669 radiographs used to train and validate the neural network, and 100 radiographs used as a test dataset [1]. All radiographs went through reading by both humans and the artificial neural network. Readers used the modified New York criteria to determine either the presence or absence of definite radiographic sacroiliitis. The researchers then analysed whether the human readers or artificial neural network agreed.

The artificial neural network achieved excellent performance in accurately recognising definite radiographic sacroiliitis in these patients, with high ratings of sensitivity and specificity (0.90 and 0.93 for the validation and 0.87 and 0.97 for the test set). This artificial intelligence-driven model could enable accurate detection of sacroiliitis for both diagnosis of patients in the clinic and classification of axSpa when selecting patients for clinical trials.

"I do think that the developed artificial neural network might be helpful in clinical practice," Prof. Poddubnyy concluded. This approach will now be tested for the assessment of MRI of sacroiliac joints, which would be especially relevant for the diagnosis of axSpa in an early stage.

1. Bressem KK, et al. Development and validation of an artificial intelligence approach for the detection of radiographic sacroiliitis. 2018, ACR Convergence 2020, 5-9 Nov.

Resolution of dactylitis or enthesitis is associated with improvements in joint and skin symptoms

An analysis of the DISCOVER-1 and DISCOVER-2 trials revealed that guselkumab led to a significant resolution of dactylitis and enthesitis in patients with active psoriatic arthritis. Resolution of these key symptoms was associated with ACR20/50/70 and PASI75/90 response.

The selective IL-23 blocker guselkumab demonstrated efficacy in patients with active psoriatic arthritis (PsA) in the two phase 3 trials DISCOVER-1 (NCT03162796) and DISCOVER-2 (NCT03158285) [1]. Dactylitis and enthesitis are both key PsA clinical manifestations that can be difficult to treat and increase the disease burden. In a pooled analysis of the DISCOVER-1 and -2 trials including 1,100 patients, relationships between improvements in dactylitis or enthesitis and other PsA domains in patients with dactylitis or enthesitis at baseline were assessed.

At baseline, 42% of the pooled patients had dactylitis (assessed in a total score 0-60) and 65% had enthesitis (assessed in the Leeds Enthesitis Index). At week 24, guselkumab in both doses significantly improved dactylitis (see Figure) and enthesitis scores compared with placebo. Rates of dactylitis or enthesitis resolution by week 24 were consistently significantly associated with ACR20/50/70 and PASI75/90 response (P<0.001). At week 24, significant correlations were observed between dactylitis change scores and PASI. As Prof. Dennis McGonagle (University of Leeds, UK) pointed out during the presentation, improvement in dactylitis by guselkumab was also associated with improved mental health. Likewise, improvements in enthesitis index score correlated with improved physical function.

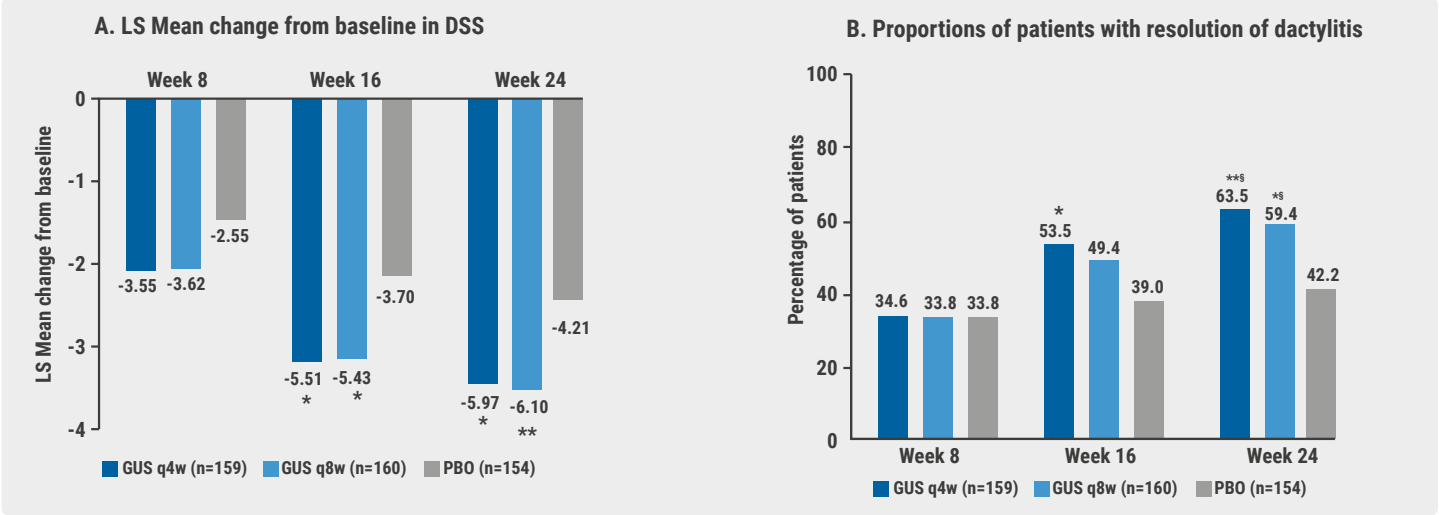
1. McGonagle D, et al. Effects of guselkumab, a monoclonal antibody that specifically binds to the p19-subunit of interleukin-23, on dactylitis and enthesitis in patients with active psoriatic arthritis: pooled results through week 24 from two phase 3 studies. 0895, ACR Convergence 2020, 5-9 Nov.

Promising novel treatment option for psoriatic arthritis

The small molecule deucravacitinib led to a significantly better ACR20 response and better physical function independent of prior TNF inhibitor use in 180 psoriatic arthritis patients in a randomised, double-blind, placebo-controlled phase 2 trial.

Deucravacitinib (formerly BMS-986165) is a novel oral tyrosine kinase (TYK)2 inhibitor. It is far more selective than other drugs in this class, as it does not bind to the kinase domain, but only to a regulatory domain of TYK2 outside the active site [1]. Thus, it inhibits downstream pathways important in psoriasis and psoriatic arthritis (PsA) pathophysiology, including interleukin (IL)-23 and IL-22, while limiting off-target effects observed with other

Figure. Pooled DISCOVER-1 & 2: Improvement/resolution of dactylitis through week 24 among patients with dactylitis at baseline



Unadjusted (nominal) *P<0.01, **P<0.001 versus placebo.
§ Adjusted P<0.05 versus placebo.
LS, least squares; DSS, Dactylitis Severity Score; GUS, guselkumab; q4w, every 4 weeks; PBO, placebo.

kinase inhibitors. In an earlier phase 2 dose-finding study in psoriasis, this drug showed to be significantly more effective compared with placebo: 67-75% of patients treated with ≥3 mg deucravacitinib achieved a ≥75% reduction from baseline in Psoriasis Area and Severity Index (PASI)75 at 12 weeks (vs 7% with placebo; P<0.001) with only mild-to-moderate adverse events. During the meeting, Prof. Philip J. Mease (University of Washington, USA) presented results from the initial 16-week placebo-controlled phase of a phase 2 trial (NCT03881059) that evaluated the efficacy and safety of the selective TYK2 inhibitor in patients with active PsA.

The 16 weeks of treatment were completed by 180 of 203 patients (89%). Baseline characteristics were comparable between all groups. An inadequate response to TNF inhibitors was observed in 15% of patients. Both deucravacitinib 6 and 12 mg demonstrated significantly greater ACR20 responses (primary endpoint) versus placebo (52.9% and 62.7% versus 31.8%, respectively). The selective TYK2 inhibitor was also superior regarding ACR50 and ACR70 improvement. Significant results were observed regardless of previous TNF inhibitor exposure or body weight (<90 kg vs ≥90 kg). Moreover, functional improvements (assessed using the Health Assessment Questionnaire–Disability Index) were significantly more pronounced in both deucravacitinib doses compared with placebo. Moreover, the treatment led to an increased quality of life and a resolution of enthesitis, while psoriasis-related and composite outcomes were improved compared with the placebo group.

The treatment was generally well tolerated with a safety profile consistent with that observed in the earlier psoriasis trial. "These results suggest that deucravacitinib may be a promising treatment for patients with active PsA and support its continued clinical development for this disease," Prof. Mease concluded. Overall, it will be interesting to see whether TYK2 inhibition that selectively interferes with the PsA disease-associated IL-23/IL-17 axis will compare against pan-JAK or predominantly JAK1 inhibitors.

1 Mease PJ, et al. Efficacy and safety of deucravacitinib (BMS-986165), an oral, selective tyrosine kinase 2 inhibitor, in patients with active psoriatic arthritis: results from a phase 2, randomized, double-blind placebo controlled trial. L03, ACR Convergence 2020, 5-9 Nov.

How to Diagnose Large Vessel Vasculitis: Promises and Pitfalls

How to choose imaging modalities in large vessel vasculitis

Different types of imaging in large vessel vasculitis have specific characteristics which should be known to make an informed decision on which modality to use for monitoring disease activity.

Regular monitoring of disease activity in large vessel vasculitis is recommended by American and European guidelines [1]. Monitoring can be performed with inflammatory markers and imaging. It is now known that new lesions may form despite sustained clinical and laboratory remission, as shown by autopsy findings that demonstrate ongoing vascular inflammation even in patients in clinical remission. Thus, information about the vessel wall is needed to identify inflammation before the damage has occurred.

Ultrasound, MRI/magnetic resonance angiography (MRA) and fluorodeoxyglucose (FDG) PET/CT are modalities that can be used to monitor disease activity. Ultrasound has the advantages of being non-invasive and inexpensive. New stenosis or wall thickening (suggesting active disease) and the response to treatment can be detected with ultrasound. The halo sign disappears between 2 days and several weeks, especially in cranial vessels, but wall swelling can persist in larger extracranial arteries for months to years. Ultrasound has many advantages: it can be done at the bedside, is inexpensive, non-invasive, and can visualise axillary arteries. However, it cannot assess vessels behind bone, and it is limited by sonographer expertise and resolution of the machine.

MRI/MRA provides a look into the lumen and the vessel wall, having the potential to identify vascular stenosis, occlusions,

aneurysms, ectasia, and mural thickening. It provides information on disease extent, damage, and activity, and does not involve radiation or iodinated contrast. Nonetheless, in a study, it did not correlate with clinical disease activity and >50% of patients in clinical remission had active disease by MRA. MRI visualises the aorta and is cheaper and more accessible than FDG PET/CT. On the other hand, cranial and large vessels cannot be imaged sufficiently in one examination. Besides, there are the known contraindications of MRI (e.g. pacemakers) and the higher costs compared with ultrasound.

FDG PET/CT monitoring evaluates cellular metabolic changes in the inflamed vessel wall as opposed to morphologic changes caused by inflammation. It is more sensitive than MRA for disease activity and uptake may predict increased risk for relapse. Also, PET uptake may reflect response to treatment changes. The disadvantages of FDG PET/CT include the fact that it may not adequately show the lumen. Furthermore, its availability is limited, it is expensive, and there is a lack of consensus of cut-off criteria for inflammation. Radiation is emitted to the patient when using CT, and it cannot be used in patients with elevated blood glucose. Finally, it is unclear whether to escalate treatment based on PET alone. Dr Anisha Dua concluded by saying that imaging can add information outside of clinical assessment in large vessel vasculitis. Imaging modalities, new methods and tracers need to be incorporated into clinical trials to generate evidence and to better understand the significance of specific findings.

1. Dua AB. Role of Imaging in Treatment and Follow-Up for Patients with Large-Vessel Vasculitis. 2F053, ACR Convergence 2020, 5-9 Nov.

Diagnosis of large vessel vasculitis with imaging

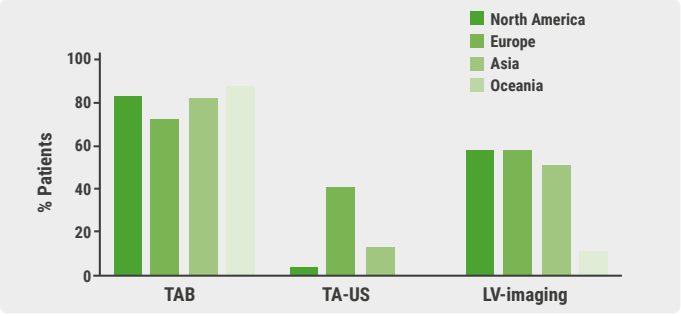
Imaging plays an important role in establishing the diagnoses of both Takayasu's arteritis and giant cell arteritis. The landscape of possibilities is evolving, and the advantages and disadvantages of different investigations have to be weighed.

In large vessel vasculitis, it is important to understand the limitations of traditional evaluations and to know in what way inflammation may be recognised on different imaging modalities [1]. This talk focused more on the disease entities of Takayasu's arteritis and giant cell arteritis which share many pathological similarities.

Takayasu's arteritis is a disease that presents with many different imaging faces. In terms of choosing between the different possible types of angiography that may be performed to diagnose Takayasu's, Dr Peter Grayson (National Institutes of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIH, USA) reflected on several considerations. In general, he rated CT angiography (CTA) and magnetic resonance angiography (MRA) as equivalent. An advantage for the MRA is of course the avoidance of radiation which can be particularly valuable in younger patients. Another aspect to consider in MRA is possible long retention of gadolinium that has been found in different tissues. In any case, Dr Grayson endorsed avoidance of catheter-based angiographies and measurement of central artery pressure in Takayasu's disease.

The use of temporal artery biopsies (TAB) to diagnose giant cell arteritis (GCA) can also be seen as a medal with 2 sides: on the plus-side, there is tissue-level confirmation, documented findings with a possibility for direct review, and the historically accepted role of TAB as the gold standard. Limitations of TAB include the possibility of missing skip lesions, some cases of CGA in which the temporal arteries are not affected, and the fact that TAB is invasive, expensive, and open to subjective interpretation. Dr Grayson also mentioned that the sensitivity of temporal artery biopsy is declining. He pointed out that large vessel GCA –an increasingly recognised phenotype– may or may not have cranial features of the disease. It includes on one hand less risk for vision loss, but on the other risk for more relapsing and refractory disease. Currently, multi-modal assessment in GCA is being performed in many parts of the world (see Figure). In a large study with 941 GCA patients, 25% had no TAB, 27% of TABs were negative, and 47% positive.

Figure. Use of multi-modal assessments in the diagnosis of GCA [1]



GCA, giant cell arteritis; TAB, temporal artery biopsies; TA-US, temporal artery ultrasound; LV, large vessel.

In summary, Dr Grayson made recommendations for diagnostic imaging in patients with (suspected) GCA, stressing the fact that these were all conditional: TAB is endorsed over temporal artery ultrasound and MRI of cranial arteries. In case of negative biopsy, non-invasive large vessel imaging can aid in diagnosis over clinical assessment alone. Finally, in newly diagnosed GCA, non-invasive vascular imaging can be of help in evaluating large vessel involvement.

1. Grayson P. Large Vessel Vasculitis Imaging: Promises and Pitfalls. 2F053, ACR Convergence 2020, 5-9 Nov.

Osteoarthritis – Novel Developments

Knee osteoarthritis patients with indicators of inflammation could profit from methotrexate

Patients with osteoarthritis and signs of inflammation showed benefit when treated with methotrexate. In a new trial, improvements were observed in both systemic markers of inflammation and also joint function.

The concept of local as well as systemic inflammation increasing joint impairment in osteoarthritis (OA) seems increasingly acknowledged [1]. "We see patients with OA almost every day who are usually advised non-pharmacological interventions and analgesics only, until the pain is unbearable and then they are asked to go for knee replacement," Prof. Biswadip Ghosh (Institute of Post Graduate Medical Education and Research, India) described the current situation [2]. "Most patients suffering from knee OA have episodes of inflammation and each episode not only increases the pain but also further damages the joint," he further pointed out.

The presented trial assessed the efficacy of methotrexate versus glucosamine as a substitute for placebo in adults with primary radiographic-confirmed OA of the knee and joint swelling as well as pain for ≥6 months.

Based on erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels at baseline, 249 patients were assigned to an inflammatory group (n=172) or a non-inflammatory group (n=77). Among the exclusion criteria were Kellgren and Lawrence grade-4 OA, recent intra-articular injections, and uncontrolled metabolic conditions such as diabetes or gout.

Patients assigned to the inflammatory group of the trial had either increased ESR (>30 mm/hour) and CRP (>1.5 times the reference value) on 1 occasion or 1 of the parameters measured at 2 separate moments that were 1 month apart. Patients in this group also underwent further diagnostic imaging with musculoskeletal ultrasound, X-ray, and MRI. Patients in the inflammatory group were then randomised to treatment with methotrexate or glucosamine with a follow-up time of 3 months.

Baseline demographics showed a mean age of 51.9 versus 51.6 and a Western Ontario and McMaster Universities Arthritis Index (WOMAC) of 45.20 versus 49.356 in the non-inflammatory versus the inflammatory group, respectively.

Within the methotrexate-treated part of the inflammatory group, ESR was significantly decreased compared with baseline (P=0.0007). Moreover, WOMAC decreased from a mean of 52 at baseline to a mean of 38 after methotrexate treatment (P<0.0001), indicating better physical function. In the patients in the inflammatory group that were treated with glucosamine, changes in ESR and WOMAC were not significant.

"In conclusion, we should look for inflammation in symptomatic primary knee OA patients and if found, we should treat it with anti-inflammatory agents," recommended Prof. Gosh. He suggested that methotrexate may be considered in such patients if conventional treatments fail, but also pointed to the need for more research regarding the role of inflammation in knee OA patients.

1 Scanzello CR, Loeser RF. Arthritis Rheumatol. 2015;67:2797-800.
2 Gosh B, et al. Comparison of Methotrexate and Glucosamine in Primary Knee Osteoarthritis with Inflammation. P1648, ACR Convergence 2020, 5-9 Nov.

Anticoagulation with vitamin K antagonist is associated with risk of knee and hip replacement

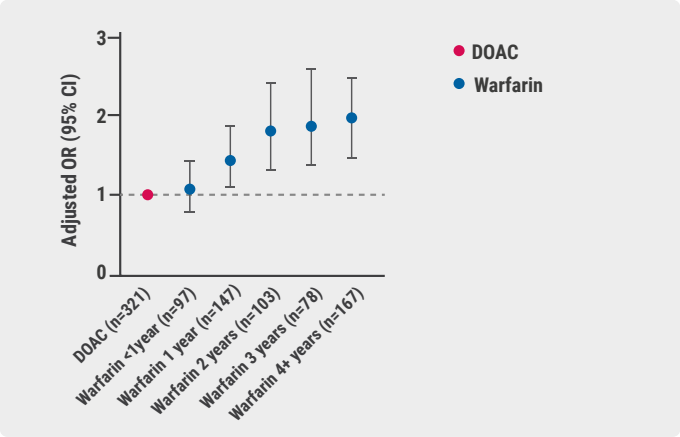
In contrast to those with direct oral anticoagulation, patients suffering from osteoarthritis using vitamin-K antagonist warfarin had a higher risk of needing knee or hip replacement in a case-control study.

"Currently, we have no disease-modifying treatment available, with joint replacement reserved for end-stage disease," Dr Priyanka Ballal (Boston University Medical Center, USA) stated concerning osteoarthritis (OA) [1]. She pointed out that vitamin K plays a role in coagulation and that several proteins in bone and cartilage depend on it. "Inadequate levels of vitamin K have been shown to cause abnormal joint tissue mineralisation and contribute to the incidence of OA," she continued to explain. The current study aimed to find out if antagonising vitamin K by warfarin would increase OA progression.

Using data from The Health Improvement Network, a nested case-control study was performed that included 913 patients with knee and hip replacement. These patients were matched by age and sex to 3,652 controls. This UK database contains medical records from general practitioners and is representative of the general population. Patients were enrolled between 2009 and 2018 and were adults aged 40-80 years that were treated with warfarin or direct oral anticoagulants (DOAC) for atrial fibrillation. Among the exclusion criteria were severe co-morbidities restricting surgery, knee replacement, or hip replacement before 2014 and warfarin or DOAC use within 1 year before the study. By performing a conditional logistic regression, results were controlled for confounders.

Mean age of the study subjects was 75.1 years, 48% were female. Warfarin was given to 64.8% of the cases, while 35.1% received DOAC. Among the controls, the rate of warfarin users was 56.3% and 43.6% received DOAC. The results showed that the confounder-adjusted risk for knee replacement or hip replacement was 57% higher in the warfarin-treated patients (adjusted odds ratio 1.57, 95% CI 1.30–1.89). Compared with DOAC intake, drug exposure to warfarin increased the risk over time. A higher risk was still significant in further adjusted analyses that accounted for other reasons for hip replacement than OA. "We found an incremental risk of hip and knee replacement with the duration of warfarin use," Dr Ballal further pointed out. In those with warfarin use over 4 years, the risk of requiring hip replacement or knee replacement increased 2-fold (see Figure).

Figure. Gradual increase of risk for hip or knee replacement with duration of warfarin use [1]



DOAC, direct oral anticoagulants.

"Given the prevalence and impact of OA, our data, along with the existing literature, support the need for a well-powered randomised controlled trial evaluating vitamin K supplementation in OA. Our study also raises the consideration of using DOACs over warfarin when indicated in people with or at risk of OA," she concluded.

1. Ballal P, et al. Warfarin Use and Risk of Knee and Hip Replacements. S0934, ACR Convergence 2020, 5-9 Nov.

Osteoporosis – New Data

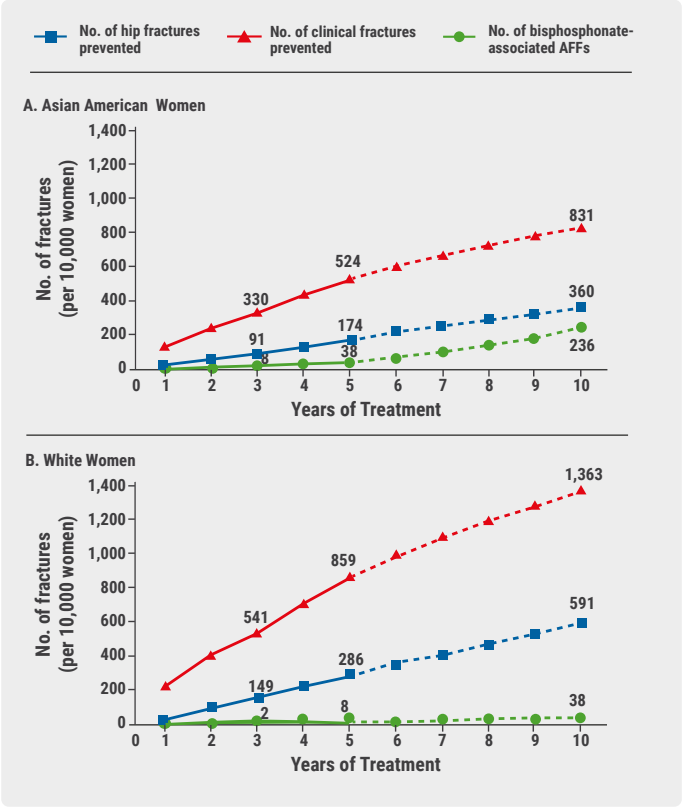
Bisphosphonate use: Asian American women have a smaller treatment benefit

A large observational study showed that the reduction of clinical fractures by bisphosphonates outweighs the risk of bisphosphonate-associated atypical femur fractures. However, Asian Americans have a higher risk for these fractures, thus diminishing their advantage of therapy, in particular in the long term.

Concerning patient safety, Prof. Jinoos Yazdany (University of California San Francisco, USA) selected a study on bisphosphonates in her lecture 'Year in review' as particularly relevant for daily practice [1]. Although bisphosphonates are effective in reducing osteoporotic fractures, concerns about atypical femur fractures (AFFs) have contributed to substantially decreased bisphosphonate use. To further explore these uncertainties, a large observational study was performed including 196,129 women ≥50 years of age that received bisphosphonates [2]. All patients were members of the Kaiser Permanente Southern California healthcare system and were followed for a period of >10 years. The primary outcome was AFFs. Data on risk factors, including bisphosphonate use, was obtained from electronic health records. "What I liked about this study is that they radiographically adjudicated AFFs, which is a methodologic improvement over previous studies," Prof. Yazdany said. There were large numbers of Asian American and Latinx patients in the whole population.

In total, 277 AFFs occurred. Indeed, the use of bisphosphonate increased the risk of AFFs. The incidence of fractures increased with a longer duration of bisphosphonate intake with a substantial increase in risk about the 5-year mark, a time point where many colleagues consider a drug holiday. "The most interesting finding of this study was that the risk for AFFs was much higher in Asian American women compared with other ethnic groups," said Prof. Yazdani. Asian American women had a 4.84-fold elevated risk (95% CI 3.57–6.56) compared with White women. Bisphosphonate discontinuation was associated with a rapid decrease in the risk of AFFs. Decreases in the risk of osteoporotic and hip fractures during 1–10 years of bisphosphonate use far outweighed the increased risk of AFFs in White women. However, the benefit was less pronounced among Asian American women, especially after 10 years. "After 10 years the number of prevented hip fractures (360) and AFFs (236) almost converge, so I believe we have to think about drug holidays for this patient group," Prof. Yazdani concluded.

Figure. The number of clinical fractures prevented by bisphosphonates outweighs the risk of biphosphonate-associated AFFs in all ethnicities. However, Asian Americans have a considerably smaller treatment benefit. Adapted from [2]



AFFs, atypical femur fractures.

1. Yazdany J, Atypical Femur Fractures risk with bisphosphonates. 1T001, ACR Convergence 2020, 5-9 Nov.
2. Black MD, et al. New Engl J Med 2020;383:743-53.

Inflammatory disease as a risk factor for fractures

An Italian cohort study in women with inflammatory diseases such as rheumatoid arthritis discovered an increased fracture risk that was not associated with the use of corticosteroids.

"We all know that glucocorticoid-induced osteoporosis is the most common form of secondary osteoporosis and is associated with an increased risk of fragility fracture," stated Dr Giovanni Adami (University of Verona, Italy) [1]. "Nonetheless, we use glucocorticoids in several inflammatory diseases and, currently, the independent role of the inflammation or glucocorticoid use on fracture risk in such patients is still unknown," he continued to explain the motivation for the current retrospective, observational cohort study.

Data was collected from the Italian web-based nationwide tool for fracture risk assessment, DeFRAcalc [2]. The analysis was performed by propensity score matching in a cohort of 59,950 women, ~10,000 of them suffering from comorbidities including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriatic arthritis, chronic obstructive pulmonary disease (COPD), and neurologic diseases [1]. Among these, SLE and RA were most commonly linked to the use of glucocorticoids.

The mean age of study subjects was 65.1 in those not taking glucocorticoids and 65.3 in the group that took ≥5 mg of the glucocorticoid prednisone for >3 months. The BMI in these 2 groups was 24.19 and 24.92, respectively. The analysis was adjusted for age, bone mineral density, menopausal status, and family history of fragility fractures. The overall risk of vertebral or hip fracture had an adjusted odds ratio (aOR) of 1.56 for patients using glucocorticoids for >3 months compared with non-users. Interestingly, even for participants <40 years of age with >3 months of glucocorticoid use, this fracture risk was increased by ~30% (aOR 1.31). For non-vertebral/non-hip fractures the all-age aOR was about 1.24.

Furthermore, independent associations for fractures and certain diseases were identified: COPD and neurological disease were linked to both vertebral and non-vertebral fractures, while RA was associated with non-vertebral, non-hip fractures. These associations were independent of bone mineral density and glucocorticoid intake. The results indicate the deleterious effects that systemic inflammation may exert on the bone.

1. Adami G, et al. Risk of Fracture in Patients with Different Glucocorticoid Requiring Diseases. P0120, ACR Convergence 2020, 5-9 Nov.
2. https://defra-osteoporosi.it/

Best of the Posters

No progression of osteoarthritis with corticosteroid injections

A study presented during the meeting found that corticosteroid injections do not accelerate progression to total knee replacement compared with hyaluronic acid injections.

A recent cohort study suggested a 3-fold higher risk for knee osteoarthritis (OA) progression with the use of corticosteroid (CS) injections, a popular treatment recommended by guidelines. Recipients of CS injections might have more advanced knee OA, which in itself is a risk factor for OA progression, making a comparison of those undergoing CS injections to those who do not questionable, despite statistical adjustments.

Therefore, the current study aimed to explore whether CS injections are associated with increased rates of knee OA progression compared with hyaluronic acid (HA) injections that have not been associated with cartilage loss [1]. "The treatment options for knee OA are limited. Steroid injections are considered a safe and effective intervention for relieving pain from knee OA. Clinicians and patients need to know if steroid injections are making knee OA worse," Dr Justin J. Bucci (Boston University School of Medicine, USA) explained. Therefore, Dr Bucci and his coworkers used data from 2 large cohort studies of people with knee OA (MOST and OAI) who received either CS or HA injections. They reviewed the rates of radiographic progression and total knee replacement surgery. Patients in the first cohort had medical visits every 12 months, and those in the second cohort had visits every 30 months. Their exams included knee X-rays and questions about their CS or HA injections over the previous 6 months. Knee OA progression was assessed with Kellgren and Lawrence grades (KL) 0-4 and joint space narrowing (JSN) 0-3 in both studies. In OAI, medial joint space (JWS250) was also measured.

Patients with very advanced OA progression (baseline KL 4 score) and those who had received either CS or HA injections in the past were excluded from the study. X-rays from each patient's medical visits before their first injection were compared to those taken after their last injection. Annualised deterioration rates were calculated for KL, JSN, and JWS250. Multivariable linear regression was used to adjust for known risk factors of OA, including age, sex, BMI, and baseline KL grade.

The researchers analysed 792 knees, including 647 treated with CS injections and 145 with HA injections. They found that the rate of total knee replacement surgery was greater among patients with a single exam in which they reported HA injection compared with those with a single exam in which they reported CS injection (P=0.04). There was no difference between patients reporting injections at multiple exams. Multivariable analysis showed similar rates of X-ray progression for both kinds of injection treatment at either single or multiple medical exams.

The authors concluded that CS injections for knee OA were not associated with a higher rate of radiographic progression or progression to a total knee replacement compared with HA injections. Future research will focus on MRI of knees undergoing treatment with CS injection for OA to better understand its effect.

1. Bucci JJ, et al. Progression of knee OA with use of intra-articular corticosteroids vs hyaluronic acid. P1652, ACR Convergence 2020, 5-9 Nov.

No elevated risk for influenza AE in tofacitinib-treated RA patients

A posthoc analysis covering 14-15 influenza seasons revealed that influenza adverse events were similar between rheumatoid arthritis patients treated with tofacitinib, adalimumab, methotrexate, and placebo.

A previous study has shown that rheumatoid arthritis (RA) is associated with an increased incidence of seasonal influenza and its complications [1]. The COVID-19 pandemic highlights the need to understand how RA itself and its therapy can influence acute respiratory RNA viral infections. To evaluate how this risk is influenced by therapy with tofacitinib, a posthoc analysis from 21 phase 1–3b/4 studies and 2 open-label, long-term extension studies from 2005-2019 with RA patients was performed, which covered a total of 14–15 influenza seasons [2]. Data was analysed from 2 cohorts: in the phase 2–3b/4 cohort, patients received tofacitinib as monotherapy or with background DMARDs (adalimumab or methotrexate). In the overall cohort, patients received ≥1 dose of tofacitinib, as monotherapy or with background DMARDs, in phase 1–3b/4 and long-term extension studies. Included were 7,964 patients, of which 496 reported influenza.

Incidence rates for influenza adverse events (AEs) generally appeared similar across treatment arms in the phase 2-3b/4 cohort. In the overall cohort, different tocilizumab doses (total daily dose of <15 or ≥15 mg) were compared. Again, overall incidence rates were comparable across doses and age groups. Nine (1.8%) patients had serious influenza AEs, 8 were hospitalised and 2 died, both had risk factors for influenza mortality. In the majority of patients with influenza AEs, the dose of tofacitinib was not changed.

The mean number of days to the resolution of influenza AEs was numerically similar irrespective of the medication. The authors concluded that the majority of RA patients taking tofacitinib with or without DMARD experience only mild-to-moderate influenza AEs. These findings are very reassuring to the rheumatology community whose interest in viral respiratory disease has been sharply focused in 2020.

1. Blumentals W, et al. BMC Musculoskelet Disord 2012;13:158.
2. Winthrop, K, et al. Influenza adverse events in patients with rheumatoid arthritis in the tofacitinib clinical program. L04, ACR Convergence 2020, 5-9 Nov.

Hydroxychloroquine use: no indication for arrhythmias in RA and SLE patients

Hydroxychloroquine use is not associated with QTc-length prolongation, even when given in combination with other QTc-prolonging medications. This was demonstrated in an analysis of 681 patients with rheumatic disease.

Hydroxychloroquine (HCQ) plays an essential role in the management of both systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), both as monotherapy and combined with other DMARDS [1]. However, there was an ongoing concern regarding its cardiovascular safety. Recently, the interest increased because of an observational study of COVID-19 patients reporting that 19% of those receiving HCQ demonstrated a QTc >500 ms, including 1 torsades de pointes tachycardia [2]. "Given recent concerns surrounding HCQ use in COVID-19 patients and subsequent arrhythmic events, we wanted to examine the associations between its use and the QTc length on ECG in a large, asymptomatic cohort of RA and SLE patients," explained study co-author Dr Elizabeth Park (Columbia University Irving Medical Center, USA).

The cross-sectional study analysed data of 681 RA and SLE patients without clinical cardiovascular disease, including 2 prospective RA cohorts of 307 patients and a retrospective SLE cohort of 374 patients. In the 2 prospective RA cohorts, ECGs were performed as part of study data collection, while in the retrospective SLE cohort (n=374) ECGs were performed as part of standard-of-care. Data was adjusted for disease-specific characteristics including prednisone use and cardiovascular disease risk factors.

Of the whole study group (RA and SLE), 54% used HCQ and 44% had QTc lengths of more than 440 ms. The mean QTc length was 437 ± 28 ms. However, in the entire cohort, adjusted QTc length among HCQ users was comparable to those who did not use the drug. In multivariate logistic modelling, HCQ use was not a significant predictor of prolonged QTc. This held true for both the RA and SLE cohort. However, 9 out of 11 of the SLE patients who did have a prolonged QTc were taking HCQ. Yet, these observations were too small to detect statistically significant differences between the HCQ groups.

No significant interactions were found between HCQ and other QTc-prolonging drugs. HCQ use combined with other QTc-prolonging medications resulted in a QTc interval comparable to HCQ alone. In the SLE group, HCQ combined with antipsychotic drugs did result in longer QTc compared with using HCQ alone (441 ms vs 432 ms; P=0.014).

"Overall, the use of HCQ did not predict QTc length, even while adjusting for critical confounding factors, namely the use of other QTc-prolonging medications. Our findings reinforce the fact that HCQ remains a safe, effective long-term disease-modifying drug for our rheumatic disease patients," Dr Park concluded.

The different results seen in COVID-19 patients might be explained by the fact that these patients were critically ill. Therefore, the effect of COVID-19 itself on the heart and subsequent arrhythmia must be considered.

1. Park E. Hydroxychloroquine use was not associated with QTc length in a large cohort of SLE and RA patients. Abstract 0431, ACR Convergence 2020, 5-9 Nov.
2. Mercuro NJ, et al. JAMA Cardiol 2020;5:1036-41.

Children with rheumatic disease have no greater risk of a COVID-19 infection

A large international survey including data on 427 children demonstrated that all of them had mild COVID-19 disease, despite the intake of immunosuppressive medication. Besides, few children contracted COVID-19.

Globally, fewer cases of COVID-19 have been reported in children (0-17 years) compared with adults. Hospitalisation rates are significantly lower in children than in adults,

suggesting that children may have a less severe disease course from COVID-19. However, children with rheumatic diseases face unknown risks in the setting of the pandemic. "Early in the pandemic, we were very concerned about how COVID-19 would affect children with rheumatic diseases," Dr Jonathan S. Hausmann (Harvard Medical School and Boston Children's Hospital, USA) explained [1]. They may have an elevated risk of infection due to the underlying disease and also the medications used to treat them. "Early in the pandemic, we were receiving phone calls from worried parents wondering whether they should continue immunosuppressive drugs, because of the unknown risk that their children faced with COVID-19," Dr Hausmann said.

To get a better understanding of the impact of COVID-19 on children with rheumatic diseases, Dr Hausmann and colleagues analysed data from the international COVID-19 Global Rheumatology Alliance Patient Experience Survey. They sent surveys to parents of children with rheumatic diseases through patient support organisations and social media. Parents provided information on their child's rheumatic disease diagnosis, medications, disease activity (as measured by a visual analogue scale from 0-10), whether or not the child ever developed COVID-19, and any outcomes they experienced if they were infected. Furthermore, the parents completed a questionnaire that assessed the general well-being of the child.

In the survey, data from 3 April to 8 May 2020 was collected. Most of the 427 children (<18 years) lived in the Americas, were White, female, and 5-14 years old. The majority of patients had juvenile idiopathic arthritis (40.7%), and most were taking conventional synthetic DMARDs and/or biologic DMARDs. The median disease activity score was 3. The survey also included children with other paediatric rheumatic diseases such as lupus, dermatomyositis, and autoinflammatory diseases. Within this group, only 5 children (1.2%) were diagnosed with COVID-19, 3 through self-diagnosis and 2 physician-diagnosed based on symptoms. None required hospitalisation or had severe outcomes.

"Surprisingly, only 4.0% of families had stopped medication due to concern of immunosuppression," Dr Hausmann said. The data showed that –similar to otherwise healthy children– those with rheumatic diseases do not seem to be at greater risk of developing COVID-19 or COVID-19-related complications, even when taking immunosuppressive medications.
"Our study suggests that children with rheumatic diseases should continue their immunosuppressive drugs during the pandemic, as it does not appear to place them at an increased risk of COVID-19-related complications," Dr Hausmann concluded.

Limitations of the study are that the data were self-reported responses from parents who were engaged in social media or who were willing to fill out a survey, which may not fully represent all children with paediatric rheumatic diseases. Other studies have shown that juvenile SARS-CoV-2 infection is associated with a poorly defined multisystem inflammation syndrome in children (MIS-C) where active viral replication is usually not detectable, which is another example of the comparative resiliance of this group to severe COVID-19 disease [2].

1. Hausmann JS. Impact of the COVID-19 pandemic among children with rheumatic diseases from around the globe. P1685, ACR Convergence 2020, 5-9 Nov.
2. Feldstein LR, et al. N Engl J Med 2020;383:334-346.

Insufficient antimalarial supply for rheumatic disease treatment in the early COVID-19 pandemic

According to the results of a survey, the use of antimalarial drugs for COVID-19 patients during the early pandemic led to a shortage of hydroxychloroquine and chloroquine as long-term treatment for patients with rheumatic diseases.

"Early in the COVID-19 pandemic, hydroxychloroquine and chloroquine were promoted for treatment and prevention of SARS-CoV-2 infection, despite little evidence for their efficacy," said Ms Emily Sirotich (COVID-19 Global Rheumatology Alliance Steering Committee and McMaster University, Canada) [1]. Based on data from the COVID-19 Global Rheumatology Alliance Patient Experience survey, the prevalence and impact of antimalarial drug shortages were assessed. Furthermore, the potential link between the use of antimalarial drugs and a decreased risk of a SARS-CoV-2 infection in rheumatoid arthritis patients was studied.

Anonymously, 9,393 patients entered data about the type of their rheumatic disease diagnosis, medication, COVID-19 status, and disease activity, as well as information about physical and mental health via the Patient-Reported Outcomes Measurement and Information System (PROMIS).

The participants had a mean age of 46.1 years, 90% were female, 41.2% used medication containing antimalarials, and the most common diagnoses were systemic lupus

erythematosus (38.9%) and rheumatoid arthritis (38.6%). A positive COVID-19 status was reported by 5.5% (n=519) overall; 6.7% in the group using antimalarials and 4.7% in those only using other drugs. Of the COVID-19-positive study subjects treated with antimalarials, 10.8% were hospitalised and 13.1% received antimalarials as COVID-19 treatment.

"In summary, 6.2% of patients taking antimalarials were unable to continue taking their medication, due to a lack of supply of their pharmacy," Ms Sirotich summarised. In contrast to patients not on antimalarials, these patients had significantly higher activity of their rheumatic disease, worse physical, and poorer mental health (P<0.001 for all comparisons). Moreover, taking antimalarials for rheumatic disease did not protect the participants from COVID-19 as such, or hospitalisation for COVID-19.

"The unintended harmful consequences of repurposing antimalarials, without adequate evidence for benefit, highlights the importance of maintaining scientific rigour even in the context of a pandemic," Ms Sirotich stressed.

1 Sirotich E, et al. Antimalarial drug shortages during the COVID-19 pandemic: results from the Global Rheumatology Alliance Patient Experience survey. P0007, ACR Convergence 2020, 5-9 Nov.

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