Psoriatic Arthritis Research Review™

Making Education Easy

Issue 8 - 2021

In this issue:

- Low risk of severe COVID-19-related outcomes in patients with IJD
- DISCOVERY-1/2: Guselkumab reduces fatigue independently of symptom improvement
- Ixekizumab continuation is necessary even in patients who achieve stable MDA
- IL-17 antagonists do not increase the risk for IBD when underlying disease severity is considered
- Risk for lower limb joint arthroplasty not mitigated by DMARDs or TNF antagonists
- OPAL trials: tofacitinib rapidly elicits significant reductions in pain
- Ultrasound valuable for assessment of PsA patients with fibromyalgia
- Using biologics to treat psoriasis may protect against PsA development
- Health related QoL impacted by comorbidities including obesity
- Non-pharmacological interventions may be efficacious for sleep disturbances

Abbreviations used in this issue:

CI = confidence interval; **COVID-19** = coronavirus disease 2019; **DMARD** = disease-modifying antirheumatic drug; **HR** = hazard ratio; **IBD** = inflammatory bowel disease; **IL** = interleukin; **IJD** = inflammatory joint diseases; **JAK** = Janus kinase; **MDA** = minimal disease activity; **NSAID** = nonsteroidal anti-inflammatory drug; **PsA** = psoriatic arthritis; **QoL** = quality of life; **TNF** = tumour necrosis factor.

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Welcome to the latest issue of Psoriatic Arthritis Research Review.

Publication of one of the secondary outcome measures – fatigue – from the phase 3 DISCOVERY-1 and DISCOVERY-2 trials in *Arthritis Research & Therapy* provides hope for patients with psoriatic arthritis (PsA) reporting an independent, clinically significant and durable reduction in fatigue following guselkumab therapy from as early as week 8 and sustained through to one year. This complements the other positive efficacy outcomes already reported for guselkumab in PsA including improvements in symptoms of musculoskeletal and cutaneous disease, enthesitis, dactylitis and health-related quality of life (QoL). We report further results from the SPIRIT series of trials regarding the use of the interleukin (IL)-17A antagonist ixekizumab in the treatment of PsA. In previous issues we have discussed the phase 3 SPIRIT-P1 and SPIRIT-P2 trials where ixekizumab demonstrated superior efficacy to both the tumour necrosis factor (TNF)-α inhibitor adalimumab and placebo, eliciting rapid and durable improvements in both articular and cutaneous disease manifestations, regardless of prior exposure to TNF inhibitors. Newly published results from the SPIRIT-P3 withdrawal study in *Arthritis & Rheumatology* finds that continuation of ixekizumab optimises disease control with high rates of disease relapse in patients who discontinue therapy after achieving a stable minimal disease activity (MDA) status. In more positive news, the trial also showed that in cases of treatment interruption, most patients can regain disease control once therapy is re-initiated. A post-hoc analysis of the phase 3 OPAL Broaden and OPAL Beyond trials published in *RMD Open* reports that in addition to the efficacy of tofacitinib for reduction of disease activity already demonstrated in PsA, it also confers clinically important improvements in pain very swiftly and durably in patients with an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (DMARDs) or TNF inhibitors. We conclude this review with a Danish meta-analysis of randomised controlled trials that reports that despite the current evidence base to support the efficacy of non-pharmacologic interventions for sleep disorders in patients with inflammatory arthritis being sparce and of low quality, interventions such as exercise, foot reflexology and auricular plaster therapy, among others, may offer an effective means to significantly improve well-being.

We hope you find these and the other selected studies interesting, that they help you to improve the lives of your patients and look forward to receiving any feedback you may have.

Kind Regards,

Associate Professor Andrew Östör
andrew.ostor@researchreview.com.au

Impact of the COVID-19 pandemic on morbidity and mortality in patients with inflammatory joint diseases and in the general population: a nationwide Swedish cohort study

Authors: Bower H et al., for the ARTIS Study Group

Summary: This study from the Swedish ARTIS (Anti-Rheumatic Therapy in Sweden) study group interrogated multiple linked nationwide registers to investigate the impact of coronavirus disease 2019 (COVID-19) on patients with immune-mediated inflammatory joint diseases (IJD). The study analysed the risks of COVID-associated hospitalisation and death in 110,567 patients with IJD in comparison to individually matched control patients without an IJD. Almost half of the IJD cohort was comprised of patients with rheumatoid arthritis (n=53,455; 48.3%) with the remainder made up of patients with spondyloarthropathies, PsA and juvenile idiopathic arthritis. Compared to absolute-all cause mortality in 2015 to 2019 amongst patients with IJD, there was an increase in 2020 but there was no increase in relative risk compared to the general population. A low but increased risk for severe COVID-19-related outcomes including hospitalisation (0.5% vs 0.3%), intensive care unit admission (0.04% vs 0.03%) and death (0.1% vs 0.07%) was seen in patients with IJD compared to controls. With the caveat that there was a low precision for particular assessments, no association between antirheumatic drugs and increased risk for inferior COVID-19-related outcomes was found.

Comment: I must say 12 months ago I thought we would be well over COVID-19. It is not the first time I have been spectacularly wrong, just ask my wife. The subject of COVID comes up with every single patient, if not just to reassure them about vaccines. This data from Sweden, a trustworthy lot, has shown that severe COVID-19-related outcomes are low in patients with IJD and in keeping with that of the general population. They were also cautiously optimistic that anti-rheumatic drugs are relatively safe in this setting. Keep calm, carry on and get everyone vaccinated.

Reference: Ann Rheum Dis 2021;80(8):1086-93
Abstract

Guselkumab demonstrated an independent treatment effect in reducing fatigue after adjustment for clinical response

Authors: Rahman P et al.

Summary: Results from two phase 3 clinical trials of 1,120 patients with active PsA published in *Arthritis Research & Therapy* demonstrate that guselkumab elicits a clinically meaningful and durable improvement in fatigue. The Janssen sponsored DISCOVER-1 (ClinicalTrials.gov Identifier: NCT03162796; n=381) and DISCOVER-2 (NCT03158285; n=739) clinical trials accrued patients with active PsA (≥ three/five swollen joints and ≥ three/five tender joints plus C-reactive protein ≥ 0.3/0.6 mg/dL in DISCOVER-1/2, respectively) and concurrent plaque psoriasis with disease unresponsive to conventional synthetic DMARDs, apremilast and/or nonsteroidal anti-inflammatory drug (NSAID) therapy from Asia, Europe, North America and Australasia. DISCOVER-1 enrolled patients with exposure of up to two TNF-α antagonists while DISCOVER-2 enrolled only biologic-naïve patients. Results showed that guselkumab at doses of 100 mg every four or eight weeks, administered subcutaneously, was efficacious for the treatment of PsA, inducing durable improvements in musculoskeletal and cutaneous symptoms as well as enthesitis, dactylitis and health-related QoL. Guselkumab improved fatigue at the end of the 24-week placebo-controlled treatment phase in both trials with significant increases in Functional Assessment of Chronic Illness Therapy-Fatigue instrument scores compared to placebo (DISCOVERY-1, mean change in fatigue scores, 5.8 vs 5.6 vs 2.2, both $p<0.001$, moderate effect size Cohen's d=0.52-0.55; DISCOVERY-2, 7.1 vs 7.6 vs 3.6, both $p<0.001$, large effect size Cohen's d=0.66-0.91). Statistically significant improvements versus placebo were seen at eight weeks in the DISCOVERY-1 trial and at 16 weeks in the DISCOVERY-2 trial. In order to quantify the proportion of fatigue reduction attributable directly to guselkumab independent of symptom improvement such as the achievement of an American College of Rheumatology response, MDA status or resolution of inflammation the researchers performed a mediation analysis. They found that the direct effect of guselkumab on fatigue accounted for between 12% to 92% of the overall impact.

Comment: I am fixated on fatigue. Such a complex entity. How on earth do we address this hydra in the few minutes available in the outpatient setting? We do know, however, that the level of fatigue in inflammatory rheumatic diseases is additive to the usual culprits. It is thus greatly welcomed to see that guselkumab, an inhibitor of the IL-23p19-subunit has a significant effect on fatigue in PsA patients which may be independent of other outcomes. Tremendous news! I do mention to patients that advanced therapies can improve fatigue so let's see how it goes. But don't forget the low hanging fruit of sleep hygiene, exercise and a healthy diet (although probably far less modifiable than we would like and it is so much easier to write a prescription).

Reference: Arthritis Res Ther 2021;23(1):190
Abstract

Withdrawing ixekizumab in patients with psoriatic arthritis who achieved minimal disease activity: results from a randomized, double-blind withdrawal study

Authors: Coates L et al., for the SPIRIT-P3 Study Group

Summary: SPIRIT-P3 was a double-blind study conducted by Eli Lilly and Company to ascertain the impact of ixekizumab withdrawal in patients with PsA who achieve a durable MDA status. The trial accrued a total of 394 patients with an established diagnosis of active disease with concomitant plaque psoriasis (active skin lesion or historical activity) from 12 countries including the US, the UK and South Africa. All patients were included in the initial 36-week open-label period and received a loading dose of 160 mg ixekizumab followed by 80 mg every two weeks. A total of 158 (40%) patients who achieved a MDA status that was sustained for at least three months participated in the withdrawal portion of the trial and were randomised between weeks 36 to 64 to undergo treatment withdrawal (placebo; n=79) or ixekizumab continuation (n=79) up to week 104. The primary outcome measure of time to relapse (defined as loss of MDA response) was significantly longer in the ixekizumab continuation group (22.3 months vs not estimable; $p<0.0001$). The secondary outcome measure of proportion of patients experiencing relapse was consistent with the primary results finding a relapse rate in the discontinuation arm of more than double that in the continuation arm (85% vs 38%). Retreatment of patients who relapsed successfully elicited a MDA status in 96% of patients at a mean time of 4.1 weeks.

Comment: It's wonderful to see withdrawal studies, who wants to be on treatment for the rest of their lives? This benefits everyone including the treasurer and he does need help right now. This study using ixekizumab in PsA showed that treatment withdrawal is possible in a proportion of patients although by far the majority relapsed. Most pleasing however, was that MDA was re-achieved in 96% of patients who had stopped ixekizumab. My advice - bite the bullet and try to wean whenever the opportunity arises (I relish, however, when the patient has already done this for me: 'Oh yeah doc, I stopped this six months ago, don't feel any different')!

Reference: Arthritis Rheumatol 2021; Mar 7 [Epub ahead of print]
Abstract

Risk of inflammatory bowel disease in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis initiating interleukin 17 inhibitors

Authors: Penso L et al.

Summary: This nationwide population-based study using the French national health data system concludes that IL-17 inhibition for IJD may not increase the risk for inflammatory bowel disease (IBD) if disease severity is considered. The research group led by Laëtitia Penso from the French National Agency for the Safety of Medicines and Health Products compared rates of new onset of either Crohn's disease or ulcerative colitis in patients with psoriasis, PsA or ankylosing spondylitis who initiated an IL-17 inhibitor such as secukinumab, ixekizumab or brodalumab (n=16,793), the conventional synthetic DMARD apremilast (n=20,556) or the TNF inhibitor etanercept (n=10,245) between 2016 and 2019. The cumulative incidence of IBD development was 0.43% (n=72) in new IL-17 inhibitor users, 0.05% (n=11) in new apremilast users and 0.48% (n=49) in new etanercept users. Although propensity score-weighted Cox and Fine-Gray modelling found an almost four-fold increased risk of IBD in anti-IL-17 users compared to apremilast users (hazard ratio [HR] 3.8; 95% confidence interval [CI], 2.1-6.8) there was no increased risk in anti-IL-17 users when compared to etanercept users (HR 0.8; 95% CI, 0.5-1.2; p=0.30). The authors commented that patients prescribed apremilast generally have milder disease with a lower inflammatory burden and therefore, the comparison of IBD risk in patients prescribed either an anti-IL-17 or anti-TNF biologic agent provides a more accurate evaluation of IBD risk according to disease severity.

Comment: The last thing a patient with autoimmune disease needs is another autoimmune disease, particularly if iatrogenic. Although there was concern regarding IL-17 antagonists and the development of IBD, this French data is informative in that there was no increased risk with IL-17 inhibitors, at least when compared with etanercept in PsA patients. This is reassuring; however, it is still probably best to avoid Il-17 inhibitors in those with past history or active IBD. Just as well the agents we have to treat PsA are increasing year on year.

Reference: Arthritis Rheumatol 2021; Jul 19 [Epub ahead of print]
Abstract

Relation of NSAIDs, DMARDs, and TNF inhibitors for ankylosing spondylitis and psoriatic arthritis to risk of total hip and knee arthroplasty

Authors: Stovall R et al.

Summary: In order to assess whether the decreased joint inflammation and bone density preservation conferred by medications used to treat ankylosing spondylitis and PsA result in a meaningful reduction in the odds of joint arthroplasty Stovall and colleagues conducted a nested case-control study of data from the US OptumLabs Data Warehouse. Analysis was made of medical therapeutics including DMARDs and TNF inhibitors, either as monotherapies or as combination regimens, received in the six months prior to joint replacement surgery in 444 adults with AS and 1,003 adults with PsA who underwent a total hip arthroplasty or total knee arthroplasty in comparison to 1,613 and 3,793 AS and PsA controls, respectively, matched by sex, age, diagnosis year, insurance type, obesity and prior joint arthroplasty. Stratification considered NSAID use. Conditional logistical regression with adjustment for confounders identified no treatment regimen that reduced the risk of joint replacement (odds ratios 0.60-1.92; none statistically significant). The authors concluded that other strategies to reduce end-stage peripheral arthritis necessitating joint surgery is required in this population.

Comment: Please note, you are not as good as you think you are until you look. Audit and self-reflection have caught me out too many times. I wasn't going to include this study in the review as I didn't believe it, then thought better of it! The analysis from a large US database has revealed that patients with ankylosing spondylitis and PsA have not been spared large joint replacement despite biologic treatment. Quel dommage! Perhaps we will realise the benefits in the next decade but this data tells us we still have a long way to go to optimise outcomes and avoid surgical intervention (let's try as our Orthopaedic colleagues certainly have enough osteoarthritis to go round).

Reference: J Rheumatol 2021;48(7):1007-13
Abstract

Median time to pain improvement and the impact of baseline pain severity on pain response in patients with psoriatic arthritis treated with tofacitinib

Authors: de Vlam K et al.

Summary: The phase 3 OPAL Broaden (ClinicalTrials.gov Identifier: NCT01877668) and OPAL Beyond (NCT01882439) trials established the efficacy of the orally administered Janus kinase (JAK) inhibitor tofacitinib for PsA with significantly improved articular symptoms at three months compared to placebo in patients with an inadequate response to conventional synthetic DMARDs or TNF inhibitors. Both trials evaluated 5 mg and 10 mg tofacitinib twice daily and had two placebo arms that crossed over to 5 mg or 10 mg tofacitinib at three months. OPAL Broaden also had an active comparator arm consisting of adalimumab 40 mg every two weeks. In this post-hoc analysis of data in patients who received 5 mg tofacitinib twice daily, placebo with three-month cross-over to 5 mg tofacitinib, or adalimumab from OPAL Broaden and OPAL Beyond (5 mg tofacitinib, n=238; placebo/ 5mg tofacitinib, n=118; adalimumab, n=106) published in *RMD Open*, de Vlam et report that tofacitinib and adalimumab confer a rapid and clinically meaningful reduction in pain that is durable. At three months a greater proportion of patients in the tofacitinib and adalimumab treatment arms achieved a much improved or very much improved pain score (defined as ≥ 30% or ≥ 50% decrease in patient-reported Visual analogue Scale pain score from baseline) compared to placebo (OPAL Broaden, ≥ 30% improvement, 56.3% vs 58% vs 34.6%, respectively; ≥ 50% improvement, 47.6% vs 41% vs 21.2%). Significant reductions in pain were observed from month 1 (OPAL Broaden, proportion of patients with a very much improved pain score, 30.5% vs ~ 38% vs 15.7%). Parametric modelling revealed a correlation between more rapid improvements in pain and more severe baseline pain in patients administered tofacitinib.

Comment: Pain, the cardinal symptom of illness. Thankfully advanced therapies tackle this head-on showing improvements in pain which occur early and persist over time. This analysis shows that the JAK inhibitor tofacitinib improves pain outcomes and works particularly well in patients with higher baseline pain. Evidence is accumulating that JAK inhibitors have a specific role in modulating pain pathways which may differentiate them from biologic drugs. Let's see what happens in the real world!

Reference: RMD Open 2021;7(2):e001609
Abstract

Role of ultrasound for assessment of psoriatic arthritis patients with fibromyalgia

Authors: Polachek A et al.

Summary: This single-centre study prospectively assessed the value of ultrasound imaging for assessment of disease activity in patients with coexisting PsA and fibromyalgia. A total of 156 consecutive patients with PsA seen at the Tel-Aviv Medical Centre in Israel between July 2018 and July 2020 were included in the study. Just over one-quarter of patients (26.9%) had coexisting PsA and fibromyalgia and the remaining three-quarters (73.1%) had PsA in the absence of concomitant fibromyalgia. All patients underwent clinical assessment utilising four composite indices: non-MDA, Composite Psoriatic Disease Activity Index, Disease Activity for Psoriatic Arthritis and Psoriatic Arthritis Disease Activity Score as well as ultrasound assessment of 52 joints, 40 tendons and 14 entheses to derive a score. Compared to patients without fibromyalgia, those with PsA and fibromyalgia had significantly higher clinical composite scores despite comparable ultrasound scores. Clinically derived measures of disease activity correlated to ultrasound scores only in the cohort of PsA patients without concomitant fibromyalgia ($p<0.001$). The authors concluded that ultrasound evaluation is more valuable than composite clinical scores for disease activity assessment in PsA patients with fibromyalgia.

Comment: How many patients have I over-treated with biological DMARDs over the years? I hate to think. Just last week I decided to MRI and bone scan a patient who had ongoing severe joint pain in whom I had tried everything. The imaging was pristine, not an inflamed joint in sight. This study from Israel confirms the benefit of imaging (in this case ultrasound) to determine the degree of inflammation in PsA patients with concomitant fibromyalgia. Turns out ultrasound is much better at discriminating disease activity than composite clinical scores. Perhaps if I had assessed for fibromyalgia in the first place, we would all be in a better place but it's so much easier to simply write another prescription….

Reference: Ann Rheum Dis 2021; Jul 2 [Epub ahead of print]
Abstract

Treating the skin with biologics in patients with psoriasis decreases the incidence of psoriatic arthritis

Authors: Flaquer M et al.

Summary: According to a retrospective cohort study conducted at the Hospital Italiano de Buenos Aires in Buenos Aires, Argentina, using biologics to treat patients with psoriasis may mitigate the risk of developing PsA. The study analysed the incidence of PsA development in a cohort of 1,719 psoriasis patients with 14,721 total patient-years of exposure to either topical treatments (81%), conventional synthetic DMARDs (13%) or biological DMARDs (6%). There were 239 cases of PsA development – 231 in patients in the topical therapy cohort, six in the conventional synthetic cohort and two in the biologic DMARD cohort - equating to a global incidence of 1.6 per 100 patient-years. Cox proportional hazards model analysis found a lower risk of PsA in patients treated with biologics versus those treated with topical therapies (incidence rate ratio=0.26; 95% CI, 0.03 to 0.94; $p=0.0111$) and adjusted analysis revealed biologics as a protective factor for PsA development with an 81% reduced risk (HR 0.19; 95% CI, 0.05-0.81). An increased risk of PsA was found in males, patients with nail involvement and those with a higher body mass index.

Comment: What a lovely little study from our colleagues in Buenos Aires, a magical place where I once tangoed the night away (and felt pretty ordinary the next day). Turns out that if dermatologists prescribe DMARDs, especially biological DMARDs, to patients with psoriasis this reduces the risk of developing PsA. Fabulous to now have some preventative data! The only problem is that dermatologists only used biological DMARDs in a piddly 6% of patients. Pathetic. If we could only encourage them to be bolder and prescribe more (on second thoughts that may reduce my patient load). Let me think about this.

Reference: Ann Rheum Dis 2021; Jul 19 [Epub ahead of print]
Abstract

Factors associated with health-related quality of life in psoriatic arthritis patients: A longitudinal analysis

Authors: Nuñez D et al.

Summary: This real-world retrospective longitudinal observational study aimed to identify factors that impact health-related QoL in patients with PsA over the course of disease evolution. A total of 230 patients diagnosed between 2007 and 2016 at the rheumatology outpatient clinic of Hospital Clínico San Carlos in Madrid, Spain, were included in the study with follow-up until November 2017 or death. Bivariable and multivariable generalised linear modelling identified older age, obesity and the presence of enthesitis at baseline as correlated with inferior health-related QoL. A negative correlation between enthesitis during follow-up and health-related QoL was also seen while methotrexate and antimalarial treatment had a positive impact.

Comment: In this world of super-specialisation patients still demand a generalist, an individual who knows them and can coordinate the orchestra of healthcare. Enter the rheumatologist. This study from Spain highlights that it is not just the musculoskeletal symptoms of PsA, especially enthesitis, that affect the patient's QoL but also their comorbidities, such as obesity. Our drugs are pretty effective at improving joint symptoms including enthesitis but we do need to embrace management of obesity to optimally improve the patient's condition. Any tips on how to do this are greatly welcomed but I now have my bariatric surgical colleague on speed dial. Let's face it, diets just don't work.

Reference: Rheumatol Ther 2021 Jul 21;8(3):1341–54
Abstract

Impact of non-pharmacological interventions targeting sleep disturbances or disorders in patients with inflammatory arthritis

Authors: Latocha K et al.

Summary: This systematic review and meta-analysis of randomised trials from a Danish group finds that the evidence base supporting non-pharmacological interventions for sleep disturbances/disorders in patients with inflammatory arthritis is not strong but that the interventions may be effective. A search of online databases including MEDLINE, CENTRAL, PsycINFO, CINAHL, ClinicalTrials.gov, ACR and EULAR with a cut-off date of September 8th, 2020 identified six trials including 308 patients with rheumatoid arthritis. In half of these trials a positive impact of the intervention was found with regards to sleep improvement – one trial found an improvement in symptoms of insomnia with auricular plaster therapy (Lu et al Med Acupunct. 2019;31[2]:130-33) while two others reported improvements in sleep quality measured using the self-reported Pittsburgh Sleep Quality Index from exercise and foot reflexology (Durcan et al J Rheumatol 2014;41[10]:1966-73 and Bakir et al Complement Ther Clin Pract. 2018;31:315-19). Meta-analysis with random effects modelling found that overall non-pharmacological interventions induced a large clinical benefit (standardised mean difference -0.80; 95% CI, -1.33 to -.028) although the quality of evidence according to GRADE (Grading of Recommendations, Assessment, Development and Evaluations) was ranked as low.

Comment: This is a call to all those young rheumatologists itching to undertake clinically meaningful research. Look no further than sleep in inflammatory arthritis! Despite well documented evidence for the benefits of adequate sleep in everyone including Rheumatic patients this is a poorly studied area particularly for non-pharmacological interventions. This review from Denmark has highlighted this fact which seems astonishing in that billions have been invested in drugs to improve the overall well-being of patients yet simple measures have not been adequately studied to improve sleep. I'm happy to help write the protocol but we could start with more exercise, less alcohol, less screen time and less out-sourcing childcare.

Reference: Arthritis Care Res (Hoboken) 2021; Jun 13 [Epub ahead of print]
Abstract

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