Rheumatology Research Review™

Making Education Easy

Issue 129 - 2021

In this issue:

Abbreviations used in this issue:

BP = blood pressure; **CV** = cardiovascular; **DOAC** = direct (novel) oral anticoagulant; **JAK** = Janus kinase; **OA** = osteoarthritis; **RA** = rheumatoid arthritis; **RCT** = randomised controlled trial; **VTE** = venous thromboembolism.

Welcome to the 129th issue of Rheumatology Research Review.

This month we begin with a small open-label study reporting positive efficacy and safety outcomes for patients with treatment-refractory active dermatomyositis treated with the JAK inhibitor tofacitinib. This is followed by two papers reporting that vitamin K antagonist use appears to be associated with OA progression. Results published in the Lancet from the Measure Up 1 and Measure Up 2 RCTs of upadacitinib for the treatment of moderate-to-severe atopic dermatitis are also included. We conclude with two papers that help to alleviate current safety concerns with treatments used in rheumatological diseases: one provides assurance that JAK inhibitors may not significantly increase the risk of VTE (venous thromboembolism), while the other discusses contrasting findings regarding CV risk associated with febuxostat use.

We hope you find this update in rheumatology research interesting. We look forward to receiving comments and feedback.

Kind Regards,

Professor Peter Youssef

peter.youssef@researchreview.com.au

Study of tofacitinib in refractory dermatomyositis

Authors: Paik JJ et al.

Summary: After a washout period, ten patients with dermatomyositis were treated with extended-release tofacitinib 11 mg/day in this open-label pilot study; all participants had disease activity predominantly located in the skin. At 12 weeks, all ten participants had achieved the primary outcome of improvement in disease activity, as defined by the International Myositis Assessment and Clinical Studies group, and 50% had experienced a moderate improvement, with the remainder experiencing a minimal improvement, according to the 2016 ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) myositis response criteria. There were also improvements from baseline in mean CDASI (Cutaneous Dermatomyositis Disease Area and Severity Index) activity score (from 9.5 to 28 [p=0.0005]) and serum CXCL9/CXCL10 levels. Three of nine skin biopsy samples showed a decrease in STAT1 signalling in association with suppression of interferon target gene expression.

Comment: Refractory dermatomyositis can be a very difficult clinical problem. This is an open-label proof-of-concept study of an extended-release tofacitinib 11mg preparation in ten patients with treatment-resistant skin disease and only one patient with resistant muscle weakness. There was an improvement in skin in all patients seen as early as 4 weeks. Seven of the ten subjects improved from moderate-to-severe skin disease to mild disease. There was an increase in strength in the one patient with resistant weakness. There were no significant adverse events, although this was only a 12-week study. It is definitely worth a try if tofacitinib can be accessed.

Reference: Arthritis Rheumatol 2021;73:858–65
Abstract

Vitamin K antagonist anticoagulant usage is associated with increased incidence and progression of osteoarthritis

Authors: Boer CG et al.

Summary: This study investigated the effect of acenocoumarol on radiographic OA progression and incidence in a cohort of 3494 participants from the Netherlands. There was an increased risk of incidence and progression for both knee and hip OA (respective odds ratios 2.34 [95% CI 1.67–3.22] and 2.74 [1.82–4.11]) in acenocoumarol recipients. Carriers of the high *VKORC1(BB)* expression haplotype together with the *MGP* (matrix Gla protein) OA risk allele in the acenocoumarol group had an increased risk of OA incidence and progression (odds ratio 4.18 [95% CI 2.69–6.50]) whereas nonusers did not (1.01 [1.78–1.33]).

Comment: Vitamin K-dependent bone and cartilage proteins are thought to be important in bone turnover and maintaining bone density. I have reviewed two studies that suggest that vitamin K analogue use is a risk factor for OA of the hip and knee, providing clinical evidence that vitamin K may be a modifiable risk factor in OA. The study population was a large prospective Dutch cohort of patients (Rotterdam Study) aged 55 years or older, and OA incidence/progression was assessed radiographically or by progression to joint replacement. In patients taking vitamin K analogues, the relative risk of developing hip OA was 2.74 and knee OA 2.34 when compared with nonusers. The usual covariates such as weight and smoking were part of the analysis. MGP is a vitamin-K dependent matrix protein, a genetic variant of which is associated with OA. The results of this study are strengthened by finding that the risk of OA was even higher in a subgroup of patients with the known *MGP* OA risk allele. The authors propose that DOACs should be used in preference to vitamin K analogues.

Reference: Ann Rheum Dis 2021;80:598–604
Abstract

Warfarin use and risk of knee and hip replacements

Authors: Ballal P et al.

Summary: This nested case-control study used a UK medical records database to identify knee or hip replacement cases (n=857; 64.6% warfarin users) among adults with atrial fibrillation prescribed either warfarin or DOACs. Cases were matched with four controls (n=3428; 56.1% warfarin users) to assess the relation of warfarin versus DOAC use to risk of joint replacement as well as duration of warfarin use. Compared with DOAC users, the risk of joint replacement was 1.59 times greater among warfarin users. Longer duration of warfarin use was associated with a higher risk of joint replacement versus warfarin use for <1 year.

Comment: This case-control study of a general practitioner database found a 1.59 relative risk of joint replacement in patients on warfarin when compared with those on DOACs, with the risk being higher in patients on warfarin for 1 year or more. These two studies provide compelling evidence that vitamin K analogues cause OA progression.

Reference: Ann Rheum Dis 2021;80:605–9
Abstract

Final report of a trial of intensive versus standard blood-pressure control

Authors: The SPRINT Research Group

Summary: Individuals at increased risk for CV disease but without diabetes or prior stroke (n=9361) were randomised to intensive BP control (target systolic BP <120mm Hg) or standard BP control (target systolic BP <140mm Hg); this paper reported the final analysis after a median of 3.33 years of follow-up. Compared with standard BP control, intensive BP control recipients had significantly lower rates of the composite primary outcome (myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure and CV-related death; 1.77% vs. 2.40% per year; hazard ratio 0.73 [95% CI 0.63–0.86]) and death from any cause (1.06% vs. 1.41% per year; 0.75 [0.61–0.92]). Participants from the intensive-treatment group had greater frequencies of serious hypotension, electrolyte abnormalities, acute kidney injury/failure and syncope events. These efficacy and safety outcomes were similar when trial and post-trial data were combined, except that there was no longer a significant between-group difference for heart failure.

Comment: CV disease remains a major cause of death in our patients, particularly those with RA and systemic lupus erythematosus. I tend to leave the management of risk factors with the GP after clarifying the risk. This study of patients aged 50 years or older at increased risk of CV disease found that targeting a BP of less than 120mm Hg rather than 140mm Hg reduced CV and all-cause mortality over a median of 3.3 years follow-up. However, this benefit came with a greater risk of hypotension and electrolyte disorders. It would be interesting to replicate this study in a large group of RA patients.

Reference: N Engl J Med 2021;384:1921–30
Abstract

Antibiotic therapy for 6 or 12 weeks for prosthetic joint infection

Authors: Bernard L et al.

Summary: Patients who had undergone appropriate surgery for a microbiologically confirmed prosthetic joint infection were randomised to open-label antibiotic therapy for 6 weeks (evaluable n=193) or 12 weeks (evaluable n=191) in this noninferiority trial. The noninferiority criterion was not met between the 6- vs. 12-week antibiotic group for the primary outcome of persistent infection (18.1% vs. 9.4%), with similar results in per-protocol and sensitivity analyses, and there was no evidence of a between-group difference for the proportions of participants with treatment failure due to a new infection, probable treatment failure or serious adverse events.

Comment: In this French study of knee and hip prosthetic joint infections, 12 weeks was superior to 6 weeks of antibiotic therapy. Patients were given a median of 9 days of intravenous antibiotics (5–15 days), which is less than the 2–4 weeks of intravenous treatment that I have seen used. Most of the treatment failures occurred after implant retention surgery. Persistent infection occurred in 18.1% of the 6-week group and 9.4% of the 12-week group. Antibiotic therapy was relatively safe with no significant between-group differences. Perhaps I should cease the antibiotics in some of my patients who are on lifelong treatment, particularly those patients who have undergone a two-stage procedure with replacement of the infected prosthesis.

Reference: N Engl J Med 2021;384:1991–2001
Abstract

Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2)

Authors: Guttman-Yassky E et al.

Summary: The phase 3 Measure Up 1 and Measure Up 2 trials randomised adolescents and adults with moderate-to-severe atopic dermatitis to receive upadacitinib 15mg (n=281 and 276, in the respective trials), upadacitinib 30mg (n=285 and 282) or placebo (n=281 and 278) once daily for 16 weeks. The coprimary endpoints of EASI-75 (≥75% improvement in Eczema Area and Severity Index score) and vIGA-AD (validated Investigator's Global Assessment for Atopic Dermatitis) response had been met by week 16 in both studies (p<0.0001), with significantly greater proportions of the respective upadacitinib 15mg and upadacitinib 30mg versus placebo groups achieving EASI-75 (70% and 80% vs. 16% in Measure Up 1 and 60% and 73% vs. 13% in Measure Up 2) and a vIGA-AD response (48% and 62% vs. 8% in Measure Up 1 and 39% and 52% vs. 5% in Measure Up 2). Both doses of upadacitinib were well tolerated, with similar incidences of adverse events or serious adverse events leading to study drug discontinuation among groups.

Comment: It is always interesting to look at studies in other conditions of medications that we feel we own as rheumatologists. Our patients often have other significant inflammatory and autoimmune conditions, and our choice of disease-modifying drug may be influenced by the effectiveness of that drug on other conditions affecting our patient. In this paper, upadacitinib 15mg and 30mg significantly improved the skin within 2–3 days in patients with moderate-to-severe atopic dermatitis. This paper read very much like a psoriasis study with the use of the EASI akin to the PASI. Approximately half of the treated patients achieved an EASI-90 and 20% achieved an EASI-100.

Reference: Lancet 2021;397:2151–68
Abstract

Independent commentary by Professor Peter Youssef, who attended Sydney University graduating with first class honours in Medicine in 1986. He then did training in Internal Medicine and Rheumatology in Sydney. Peter became a fellow of the Royal Australasian College of Physicians in 1993. He completed his doctorate in 1997 at the Flinders University of South Australia and then post-doctoral studies in Dublin returning to the University of New South Wales as a post-doctoral fellow. He is a clinical associate Professor of Rheumatology at Sydney University. Since 2007 he has been the rheumatology subeditor of the Internal Medicine Journal.

RACP MyCPD Program participants can claim **one credit per hour** (maximum of 60 credits per year in Category One – Educational Activities) **for reading and evaluating Research Reviews.**

Please CLICK HERE to download CPD Information

Etanercept or methotrexate withdrawal in rheumatoid arthritis patients in sustained remission

Authors: Curtis JR et al.

Summary: This study of 374 patients receiving combination methotrexate plus etanercept for RA sought to determine if remission (SDAI [Simplified Disease Activity Index] score ≤3.3) could be maintained on monotherapy if one of these agents was discontinued. After 24 weeks of sustained remission, the participants were randomised to continue combination therapy (n=51), discontinue etanercept (methotrexate monotherapy; n=101) or discontinue methotrexate (etanercept monotherapy; n=101). Compared with methotrexate monotherapy recipients, significantly greater proportions of etanercept monotherapy and combination therapy recipients maintained remission out to week 48 (49.5% and 52.9%, respectively, vs. 28.7% [p values 0.004 and 0.006]), and they had longer times to disease worsening (p<0.001). Remission was regained in 70–80% of participants from each treatment group who received rescue therapy. There were no new safety signals detected.

Comment: My preference has been to stop methotrexate and to continue the biologic in patients in remission on the combination. This very important paper took patients in SDAI remission on the combination of methotrexate and etanercept after 24 weeks of treatment and randomised them to methotrexate monotherapy, etanercept monotherapy or continuation of the combination for a 48-week follow-up. Within 12 weeks, about 40% of the methotrexate group and 20% of the other two groups had worsened. By 48 weeks, 28.7% of the methotrexate group, 49.5% of the etanercept group and 52.9% of the combination group remained in remission. About 70% regained remission on restarting the combination, although this took 3 months or more in a significant number. My experience has been that almost all of my patients in whom the biologic has been ceased will flare over time and that regaining remission is not guaranteed. My take from this study is to continue doing what I am doing, although I can understand the economic argument for stopping etanercept and then restarting it in those who flare, even though only 60–70% will get back into remission. Adverse events were similar across groups.

Reference: Arthritis Rheumatol 2021;73:759–68
Abstract

Non-surgical and surgical treatments for rotator cuff disease

Authors: Cederqvist S et al

Summary: In this RCT, 417 patients with rotator cuff disease and subacromial pain underwent initial rehabilitation for 3 months and MRI arthrography, and the 190 of these who remained symptomatic were randomised to nonsurgical or surgical treatments. After 2 years, both nonsurgical and surgical treatments were associated with reduced visual analogue scale pain and improved Constant Murley Score shoulder function scores, with no significant between-group difference for either of these coprimary outcomes (respective p values 0.25 and 0.077); however, there were significant improvements in pain scores and function favouring surgery among participants with full-thickness ruptures (p values 0.002 and 0.008).

Comment: This study included patients with full-thickness and non-full-thickness cuff tears, shoulder impingement, greater than 3 months of symptoms and a reduction in pain with a subacromial injection. Patients received up to 15 sessions of physical therapy over 3 months before being randomised to either surgery or nonsurgical treatment. The mean age was 56 years. Thirteen percent of the nonsurgical group underwent shoulder surgery over the 2-year follow-up period and 36% of the surgical group improved before surgery. The outcome in the surgical group was better than conservative therapy in those patients with full thickness perforating tears on MRI arthrography but not those with partial tears. My clinical practice to date has been to refer all patients with significant symptoms after adequate conservative therapy, even if they have only partial tears. I will now be less inclined to refer patients with partial tears for surgical review.

Reference: Ann Rheum Dis 2021;80:796–802
Abstract

Venous thromboembolism risk with JAK inhibitors

Authors: Yates M et al.

Summary: This was a meta-analysis of data from 42 phase 2–3 RCTs of JAK inhibitors for treating immune-mediated inflammatory diseases; 6542 JAK inhibitor patient exposure-years were compared with 1578 placebo patient exposure-years. Fifteen VTE events occurred among the JAK inhibitor recipients, compared with four among the placebo recipients. The respective pooled incidence rate ratios for VTE, pulmonary embolism and deep vein thrombosis among JAK inhibitor recipients were 0.68 (95% CI 0.36–1.29), 0.44 (0.28–0.70) and 0.59 (0.31–1.15).

Comment: I have avoided the use of JAK inhibitors in patients who are at a significant increased risk of thromboembolism, and have been proactive in recommending that patients on JAK inhibitors use VTE prophylaxis on long flights. This meta-analysis included 42 RCTs and excluded long-term extension studies. It concludes that there is not a significant increased risk of VTE on JAK inhibitors, although a small increase in risk could not be excluded. This is an area where data continue to be generated from long-term extension studies, which have generally found that the risk of VTE does not increase over time. I am becoming less concerned about the VTE risk on JAK inhibitors, but would still avoid using these agents in patients with previous significant VTE.

Reference: Arthritis Rheumatol 2021;73:779–88
Abstract

Reassessing the cardiovascular safety of febuxostat

Authors: Choi HK et al.

Summary: These authors discussed the implications of FAST (Febuxostat versus Allopurinol Streamlined Trial) for the management of gout. FAST was mandated after the CARES study (n=6190) reported increased all-cause mortality and death from CV causes in participants randomised to receive febuxostat versus allopurinol; however, a number of limitations regarding the CARES data have been expressed. FAST randomised 6128 patients with gout and ≥1 CV risk factor to continue optimal-dose allopurinol or switch to febuxostat 80–120 mg/day to achieve/maintain a serum urate level of <6 mg/dL, and followed them for a median of ~43 months. Compared with allopurinol, febuxostat in FAST was noninferior for major adverse CV events (adjusted hazard ratio 0.85 [95% CI 0.70–1.03]), and resulted in a lower risk of death from any cause (0.75 [0.59–0.95]) and lower serum urate levels. The paper's authors also discuss remaining uncertainties following publication of these FAST data, and the implications when the trial data from FAST and CARES are considered together.

Comment: This is an excellent commentary on the concerns about CV mortality on febuxostat, and it addresses the recent European Medicines Agency-mandated FAST published in 2020, which, unlike the previous FDA-mandated CARES trial, found no increase in CV mortality with febuxostat. The authors conclude that the FAST study has more internal validity as the rate of loss to follow-up was only 6% compared with 45% in the CARES study. Also, there was no CV signal in the FAST study even though the febuxostat dose was higher than in the CARES study. I found this analysis convincing and am now less concerned about the CV risk of febuxostat.

Reference: Arthritis Rheumatol 2021;73:721–4
Abstract

