Rheumatology RESEARCH REVIEW™

Making Education Easy

Issue 42 – 2021

In this issue:

Abbreviations used in this issue

ACR = American College of Rheumatology
BSR = British Society of Rheumatology
DMARD = disease-modifying antirheumatic drug
ESR = erythrocyte sedimentation rate
EULAR = European Alliance of Associations for Rheumatology
JAK = Janus kinase
OA = osteoarthritis
OR = odds ratio
RA = rheumatoid arthritis
SLE = systemic lupus erythematosus
TNF = tumour necrosis factor
VTE = venous thromboembolism

Welcome to the latest issue of Rheumatology Research Review.

In this issue, the findings of the ARCTIC REWIND trial do *not* endorse use of half-dose conventional synthetic DMARDs in patients with RA in remission, a meta-analysis provides support for using leflunomide in combination with biologic therapies in patients with RA who cannot tolerate methotrexate, and a NZ study finds that patients in the Wellington region with suspected inflammatory arthritis wait much longer to be seen than is recommended by BSR guidelines. Also in this issue, a meta-analysis finds no evidence of VTE risk with JAK inhibitors, Greek investigators develop an algorithm to assist the early diagnosis and treatment of SLE, and a phase 3 trial reports promising findings for the JAK inhibitor upadacitinib in psoriatic arthritis.

We hope you enjoy this update in rheumatology research. We always appreciate any feedback or comments you wish to send us.

Kind regards,

Associate Professor Simon Stebbings
simonstebbings@researchreview.co.nz

Associate Professor Andrew Harrison
andrewharrison@researchreview.co.nz

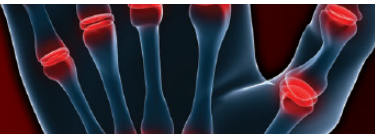
Effect of half-dose vs stable-dose conventional synthetic disease-modifying antirheumatic drugs on disease flares in patients with rheumatoid arthritis in remission

Authors: Lillegraven S et al.

Summary: The multicentre ARCTIC REWIND trial compared the effect of half-dose versus stable-dose conventional synthetic DMARDs in patients with RA in sustained remission. 160 patients with RA in remission for 12 months who were receiving stable-dose conventional synthetic DMARDs were randomised 1:1 to half-dose or stable-dose conventional synthetic DMARDs for 12 months in an open-label design. The primary end-point was the proportion of patients with a disease flare between baseline and 12 months (defined as a Disease Activity Score [DAS] >1.6, an increase in DAS score of ≥0.6 units, and ≥2 swollen joints). Flare occurred in 19 patients (25%) in the half-dose group compared with 5 (6%) in the stable-dose group (risk difference 18%, 95% CI 7–29%). Adverse events were reported in 44% and 54% of patients in the respective groups.

Comment (SS): The 'treat to target' approach in RA was successful in defining remission and identifying therapeutic strategies for achieving remission. In recent years, studies have started to explore the strategies for the maintenance of remission including possible DMARD dose reduction. There is still a paucity of evidence in this area, so studies such as this one are welcome and important. Previous studies have shown that tapering or discontinuing conventional synthetic DMARDs was associated with increased numbers of flares, but rapid reintroduction of conventional synthetic DMARDs tended to result in regaining remission. Most studies have looked at tapering biologic DMARDs but evidence for tapering conventional synthetic DMARDs alone is lacking. This study was a randomised, open-label, non-inferiority trial using the standard triple therapy regimen we are familiar with in NZ, with the half-dose group reduced to half dose at the baseline visit. Patients had to be in sustained remission for at least 12 months to be included. 25% of patients in the half-dose group flared in the study period compared with 6% in the stable-dose conventional synthetic DMARD group. This suggests a threshold effect for conventional synthetic DMARD dose, which would not surprise most clinicians. The study was open-label, with a potential for bias in the assessment of flare rates, although steps were taken to mitigate this. This study adds to the current literature including the small RETRO trial, where reduction in both conventional synthetic DMARDs and biological DMARDs to half baseline dose showed a 39% flare rate over a similar study period to this study. Such information may help to inform discussions with patients who often ask about therapy reductions. Future research needs to address the issue of how to identify patients who may best tolerate dose reduction or discontinuation, and how often to monitor such patients to 'predict flares' or intervene early.

Reference: JAMA 2021;325:1755–64
Abstract



Most appropriate conventional disease-modifying antirheumatic drug to combine with different advanced therapies in rheumatoid arthritis

Authors: Decarriere G et al.

Summary: This systematic review and meta-analysis compared the safety and efficacy of methotrexate versus non-methotrexate conventional synthetic DMARDs (e.g. leflunomide) in combination with advanced therapies (TNF inhibitors, abatacept, rituximab) in patients with RA. A literature search identified 21 studies (13 with TNF inhibitors, 3 with abatacept and 5 with rituximab) that were suitable for inclusion. Meta-analysis of data from the TNF inhibitor studies showed that the EULAR response at 6 months was lower in patients taking non-methotrexate conventional synthetic DMARDs than in those taking methotrexate (risk ratio [RR] 0.93, 95% CI 0.87–1.0; p=0.04), with a lower retention rate at 12 months. Safety and efficacy were similar between the 2 groups in the abatacept studies, but in the rituximab studies the EULAR response was better when rituximab was combined with leflunomide rather than methotrexate (RR 1.38, 95% CI 1.13–1.68; p=0.001), with similar tolerability.

Comment (AH): When RA patients progress from treatment with synthetic oral DMARDs to biologic therapy, methotrexate is usually continued in conjunction with the biologic to enhance the response. If methotrexate has been discontinued due to intolerance, other synthetic DMARDs may be prescribed, commonly leflunomide. This study undertakes a meta-analysis of published trials to determine the relative effectiveness of these two DMARDs when combined with biologic therapies. The results of the meta-analysis gave a slight advantage to methotrexate when combined with TNF inhibitors, similar results for methotrexate and leflunomide when combined with abatacept, and a small but seemingly significant advantage to leflunomide when combined with rituximab. There were insufficient data to consider the effectiveness of sulfasalazine or hydroxychloroquine. This study provides support for using leflunomide in combination with biologic therapies in patients who are intolerant of methotrexate, rather than pursuing biologic monotherapy.

Reference: Arthritis Care Res 2021;73(6):873–84
Abstract

Lupus or not? SLE Risk Probability Index (SLERPI): a simple, clinician-friendly machine learning-based model to assist the diagnosis of systemic lupus erythematosus

Authors: Adamichou C et al.

Summary: This study applied machine learning in well-characterised patient data sets to develop an algorithm to assist with diagnosis of SLE. The algorithm was developed in a cohort of 802 patients with SLE or control rheumatologic diseases, and validated in a cohort of 512 SLE patients and 143 disease controls. The SLE Risk Probability Index (SLERPI) included 14 variably weighted standard clinical and serological features. Thrombocytopenia/haemolytic anaemia, malar/maculopapular rash, proteinuria, low complement C3 and C4, antinuclear antibodies and immunological disorder were the strongest predictors of SLE. The model produced SLE risk probabilities that correlated positively with disease severity and organ damage, and a score >7 had excellent accuracy (94.8%) for identifying SLE.

Comment (SS): Diagnosing lupus can be challenging, as it often presents insidiously and with a very heterogenous clinical picture, with a mean delay in diagnosis of 10 months or longer in many studies. Classification criteria such as the Systemic Lupus International Collaborating Clinics (SLICC) and the 2019 EULAR/ACR can help in discussions with patients or by improving clinical certainty, but these are designed for use in clinical trials and although specific, lack sensitivity especially in early disease. This study included clinical data from a large cohort of lupus patients and inputted these data into a complex algorithm. Machine learning was then used to produce 14 variably weighted clinical and laboratory features that could help identify patients with SLE. The simple scoring system (SLERPI) has good sensitivity and specificity. Confirmation of the performance is needed in several cohorts and in different ethnicities. However, the SLERPI could prove a useful clinical tool in a notoriously difficult condition. The score could also help in discussions of uncertainty with patients. It is still possible to imagine, however, that the dichotomous cut-off points in the SLERPI would be less likely to help in early SLE, where features such as tenosynovitis, Raynaud phenomenon and high ESR may point to a diagnosis, but would not register in this scoring system.

Reference: Ann Rheum Dis 2021;80:758–66
Abstract

Care of patients with early inflammatory arthritis in the Wellington region according to the British Society of Rheumatology's best practice tariff standards

Authors: Farquhar HJ & Taylor WJ

Summary: This NZ study evaluated the timeliness of care of patients with suspected early inflammatory arthritis (EIA) in the Wellington region according to BSR quality standards. 117 cases of suspected EIA were included in the analysis. The median time from referral to the first appointment at a specialist rheumatology clinic was 11.4 weeks, and the median time from referral to the commencement of DMARD treatment in 61 patients with clinically confirmed EIA was 10.5 weeks. These patients attended a specialist-led clinic a median 4 times within the first 12 months. Overall, patients with suspected EIA in the Wellington region wait much longer to be seen than is recommended by BSR guidelines.

Comment (SS): Benchmarking the performance of our health service against international standards is an excellent way of identifying deficiencies in our health systems which may impact patient care. Although the UK and NZ have similar health care systems, the UK National Health Service (NHS) has historically invested far more in data collection and audit at both local and national level. Strategic benchmarking against nationally-set criteria is also a feature of the NHS, and whilst this may not always be seen as positive, it may drive quality improvements. This study by colleagues in Wellington provides a snapshot of how a typical large rheumatology department performs against the UK's quality standards developed by the BSR in 2013/14 and implemented through the UK Department of Health. The standards set out 3 targets for EIA: 1) Patients with suspected EIA should be seen within 3 weeks of referral, with those not diagnosed with EIA discharged within 6 weeks; 2) Patients with EIA should have a DMARD initiated within 6 weeks of referral and receive regular follow-up (a minimum of 4 consultant-led follow-ups over the first year of treatment) with appropriate titration of therapy; 3) Patients who meet eligibility criteria for biologics are commenced on biologics in the first year of monitoring. Despite triaging and appointments based on fast tracking patients with suspected EIA, the median time to referral and DMARD initiation was 10.5 weeks in Wellington. A UK National Early Inflammatory Arthritis Audit (NEIAA) in 2018/19 found the median time to first assessment in patients with suspected EIA was 28 days, with 38% seen within 3 weeks, and DMARD therapy initiated in 54% within 6 weeks. In Wellington, only 26% of patients were on a DMARD within 6 weeks. The authors postulate that fewer rheumatologists may be one reason for longer waiting times, and that also systems developments such as an early arthritis clinic could be helpful. It is likely that several systematic differences in health care between the UK and NZ are also important. National and local data collection in the NZ system is poor and dissemination of such information also poor. National standards of care have been avoided for many conditions, as setting expectations carries political risks. It will be interesting to see what will happen with the sweeping changes being brought in to centralise healthcare delivery through Health New Zealand from 2022. Will centrally generated data, quality standards and audit be part of this reform? In the meantime, the ability to impact on waiting times at the local level may be limited by resources, but examining local systems of triage may help to prioritise patients most likely to benefit from early therapeutic intervention.

Reference: N Z Med J 2021;134(1533):71–9
Abstract

Venous thromboembolism risk with JAK inhibitors

Authors: Yates M et al.

Summary: This meta-analysis investigated the risk of VTE in patients taking JAK inhibitors for immune-mediated inflammatory diseases. A search of Medline and Embase identified 42 randomised controlled trials that were suitable for inclusion. Data were available for 6542 JAK inhibitor patient-exposure years and 1578 placebo patient-exposure years. 15 VTE events were reported in the JAK inhibitor group and 4 in the placebo group. The pooled incidence rate ratios of VTE, pulmonary embolism, and deep vein thrombosis in patients receiving JAK inhibitors were 0.68 (95% CI 0.36–1.29), 0.44 (95% CI 0.28–0.70), and 0.59 (95% CI 0.31–1.15), respectively.

Comment (AH): JAK inhibitors are proving effective for an increasing number of immune-mediated inflammatory disorders. Concerns have been raised about a possible increase in risk of thromboembolism associated with their use, based on relatively small randomised controlled trials. This has prompted regulatory authorities in the US and Europe to issue warnings about use of JAK inhibitors in patients at risk of thromboembolism. This meta-analysis combines the available data in an attempt to determine whether the risk might be an artefact of a low number of events. There were 6542 patient-exposure years in the JAK inhibitor group and 1578 in the placebo group. The number of thromboembolic events was small; 15 versus 4, but VTE risk was not increased by JAK inhibitors. This study does not provide evidence to support the current warnings issued by regulatory authorities, and may help ensure that patients with comorbidities are not inappropriately denied access to this class of drug.

Reference: Arthritis Rheumatol 2021;73(5):779–88
Abstract

Trial of upadacitinib and adalimumab for psoriatic arthritis

Authors: McInnes IB et al.

Summary: This study evaluated the efficacy and safety of the JAK inhibitor upadacitinib and the TNF inhibitor adalimumab in patients with psoriatic arthritis. 1704 patients were randomised to receive oral upadacitinib 15mg once daily, oral upadacitinib 30mg once daily, placebo, or subcutaneous adalimumab 40mg every 2 weeks. The primary end-point was an ACR20 response (≥20% decrease in the number of tender and swollen joints and ≥20% improvement in ≥3 of 5 other domains) at week 12 with upadacitinib versus placebo. An ACR20 response was reported at week 12 in 70.6% of patients in the upadacitinib 15mg group ($p<0.001$ vs placebo), 78.5% in the upadacitinib 30mg group ($p<0.001$ vs placebo), 36.2% in the placebo group, and 65.0% in the adalimumab group. Adverse events through week 24 were reported by 66.9%, 72.3%, 59.6%, and 64.8% of patients in the respective groups.

Comment (AH): JAK inhibitors are an exciting new class of drug with potential for treatment of a range of inflammatory disorders. Establishing their relative effectiveness and safety in relation to established therapies will help determine how and at what stage they should be used. Head-to-head studies are the best way to make valid comparisons. This study compared 2 doses of upadacitinib with adalimumab and placebo, with the primary end-point of ACR20 response at 12 weeks, and the power to show non-inferiority and superiority. At 12 weeks the 30mg dose of upadacitinib was superior to adalimumab and the 15mg dose was non-inferior. The differences persisted at the 24 week time-point, and similar patterns of comparative response were seen for ACR50 and ACR70 responses. Adverse events were higher in the upadacitinib groups compared with placebo, but adverse events leading to discontinuation were similar across the 4 arms. These results should encourage longer-term trials to determine the safety and effectiveness of upadacitinib in psoriatic arthritis.

Reference: New Engl J Med 2021;384:1227–39
Abstract

Independent commentary by Associate Professor Andrew Harrison

Andrew Harrison is a rheumatologist based in Wellington, Associate Professor in Medicine at the University of Otago Wellington, and Clinical Leader of Research at Capital & Coast District Health Board. He is an Otago graduate and obtained his PhD from the Royal Postgraduate Medical School in London. His research interests include the basic cellular and molecular mechanisms of inflammation, the genetics of gout and rheumatoid arthritis, and access to healthcare resources.

Tumor necrosis factor inhibitor dose reduction for axial spondyloarthritis

Authors: Lawson DO et al.

Summary: This systematic review and meta-analysis investigated the effectiveness and safety of dose reduction of TNF inhibitor therapy in patients with axial spondyloarthritis (AxSpA) compared with usual care. A search of Cochrane Central Register of Controlled Trials, Embase, Medline, and trial registries identified 6 randomised controlled trials (n=747) that were suitable for inclusion. Compared to the standard dose of TNF inhibitor therapy, patients taking a reduced dose were less likely to have 40% improvement (risk ratio [RR] 0.62, 95% 95% CI 0.49–0.78) or partial remission (RR 0.17, 95% CI 0.06–0.46) according to Assessment of SpondyloArthritis International Society (ASAS) criteria. There were more disease flares/relapses with a reduced dose (RR 1.73, 95% CI 1.32–2.27), and no differences in infection rates.

Comment (SS): Patients with AxSpA are often young. When starting a patient on TNF inhibitor injections or infusions, it is important to consider that this will become part of their life for the foreseeable future. It is not surprising that many patients want to reduce or discontinue treatment when they feel well. How should we advise them? This meta-analysis pools data from 6 studies which have attempted to provide answers as to whether TNF inhibitors can be reduced or stopped in patients with stable AxSpA in remission, or low disease activity. The results show that there is no advantage to reducing TNF inhibitor therapy. There was a small statistically significant deterioration in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) following dose reduction (although the fall was so small as to be unlikely to be clinically significant), but the relative risk of physician-diagnosed flares was 1.73. Importantly, there was no reduction in risk of infection or other adverse events in the treatment reduction group or in local adverse reactions at injection site. The pooled studies showed the range of outcomes to have wide confidence intervals, there was some heterogeneity in outcome measures chosen, and the sample size was small. Given that the main outcome which showed inferiority was 'flare' of AxSpA, which can be subjective, it is a little surprising that the authors saw the meta-analysis as suggesting there was no benefit in dose reduction. It could easily be concluded that there was no clear evidence of inferiority in the dose reduction group in the primary outcomes. There was, however, no evidence of reduced adverse effects either. This meta-analysis suggests that a large well-conducted study with clear definition of flares is needed to answer the question of whether dose reduction is beneficial in AxSpA.

Reference: Arthritis Care Res 2021;73:861–72
Abstract

CLICK HERE
to read previous issues of Rheumatology Research Review

This Research Review has been endorsed by The Royal New Zealand College of General Practitioners (RNZCGP) and has been approved for up to 1 CME credit for the General Practice Educational Programme (GPEP) and Continuing Professional Development (CPD) purposes. You can record your CME credits in your **RNZCGP Dashboard**

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**

Independent commentary by Associate Professor Simon Stebbings

Simon Stebbings qualified from University College London. He is a Consultant Rheumatologist at Dunedin Hospital and Associate Professor at Dunedin School of Medicine, University of Otago. His research interests include the pathogenesis of ankylosing spondylitis and the development of outcome measures in rheumatic disease.

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

Authors: Boer CG et al.

Summary: This analysis of the Rotterdam study cohort investigated the effect of acenocoumarol usage on progression and incidence of OA. 3494 patients were included in the analysis. Use of acenocoumarol was found to be associated with an increased risk of OA incidence and progression (OR 2.50, 95% CI 1.94–3.20), both for knee (OR 2.34, 95% CI 1.67–3.22) and hip OA (OR 2.74, 95% CI 1.82–4.11). Acenocoumarol users who were carriers of MGP and VKORC1 single nucleotide variants had an increased risk of OA incidence and progression (OR 4.18, 95% CI 2.69–6.50) compared with non-carriers.

Comment (AH): Previous studies have found evidence of an association between warfarin use and development of OA. The validity of these observations is enhanced by a plausible biological mechanism. Warfarin causes anticoagulation through inhibition of vitamin K, which is an essential cofactor in the post-translational carboxylation of Gla proteins, rendering these proteins active. Gla proteins are not only important for coagulation, but also in bone and cartilage, particularly matrix Gla protein (MGP). A randomised trial of vitamin K supplementation in OA found no overall effect, but subjects who were deficient in vitamin K at baseline trended towards less radiographic progression of hand OA with supplementation. This study used data from the Rotterdam study to compare the incidence and progression of knee and hip OA in warfarin users compared with non-users. The main finding was that the risk of development and progression of OA was 2.5 times higher in warfarin users than non-users, with the effect seen after as little as 6 months of warfarin use. The data were adjusted for comorbidities, but there is still a risk of confounding by indication, i.e. the possibility that those who are destined to develop OA might also be at higher risk for atrial fibrillation.

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

Disease activity influences the reclassification of rheumatoid arthritis into very high cardiovascular risk

Authors: Ferraz-Amaro I et al.

Summary: This study investigated whether specific disease features influence the cardiovascular (CV) risk reclassification of RA patients. 1279 patients with RA without previous CV events, diabetes, or chronic kidney disease were assessed for RA disease characteristics, CV comorbidity, Systematic Coronary Risk Assessment (SCORE), and the presence of carotid plaque. 54% of patients had carotid plaque on ultrasound and were consequently reclassified as very high CV risk. Disease activity was also significantly associated with reclassification into a very high CV risk category. A predictive model that included dyslipidaemia and hypertension, age >54 years, and a Disease Activity Score-28 for Rheumatoid Arthritis with ESR (DAS28-ESR) score ≥2.6 yielded the highest discrimination for reclassification.

Comment (SS): An increased risk of CV disease is well established in RA. The QRisk®3 score – perhaps the most widely used CV risk score – includes RA in the algorithm and elevates the risk score accordingly, based on meta-data analysis. Beyond having a diagnosis of RA, however, it is clear that some RA patients are at higher risk than others for CV events, and this is not only related to traditional risk factors, such as smoking, dyslipidaemia and hypertension, but also to RA-associated factors, such as persistent elevations of C-reactive protein (CRP) associated with poor disease control. Our understanding of coronary artery disease (CAD) has progressed significantly in recent years. New methods of assessment such as automated coronary calcium scoring in cardiac computed tomography (CT) and chest CT are revolutionising risk assessment in asymptomatic patients or those with the newly defined chronic coronary syndrome. Carotid intimal thickening (cIMT) was found to have an association with CAD some years ago. It identifies atherosclerotic plaques and has a strong association with CAD risk and stroke. One of the strongest correlates with cIMT is advancing age, and this may explain some of the strength of the association with CAD. For this reason cIMT has fallen from favour in some units. In this study, SCORE was used and combined with CAD risk factors and markers of severity and activity in RA. The SCORE algorithm includes age, sex, smoking status, systolic blood pressure, and serum total cholesterol or total/HDL cholesterol ratio, as well as a measure of cIMT, and is calculated using SCORE risk charts. Patients were reclassified for CAD risk according to cIMT thickness. DAS28 scores, CRP and erosions score are associated with CAD risk and this is not a new finding. Patients with RA are known to be at much higher risk for CAD, and an assessment should ideally be included for all patients. Women in particular may have coronary events 10 years earlier than women without RA. This study does not add a great deal to our understanding of CAD in RA, and cIMT measures are unlikely to be used as a routine non-invasive test in most centres to stratify risk. Some important questions are worth considering. Who should be assessing and managing CAD risk in patients with RA? What is the role of newer tools such as coronary calcium scores in our patients? This study does not answer these questions.

Reference: Arthritis Res Ther 2021;23:162
Abstract

Warfarin use and risk of knee and hip replacements

Authors: Ballal P et al.

Summary: This nested case-control study in UK general practice evaluated the risk of knee and hip replacements in patients taking warfarin or direct oral anticoagulants (DOACs) for AF. 857 cases with knee or hip replacement and 3428 age- and sex-matched controls were included. Conditional logistic regression analysis revealed that warfarin users had a significantly higher risk of joint replacement than DOAC users (adjusted OR 1.59, 95% CI 1.31–1.92). A longer duration of warfarin use was associated with a higher risk of joint replacement than shorter (<1 year) use.

Comment (AH): This study looks further into the potential causative link between warfarin and OA. It addresses the possibility of confounding by indication by ensuring that the case group had the same indication for anticoagulation use as the control group. Warfarin users were compared with those taking DOACs which can be used in place of warfarin but do not inhibit vitamin K. Data on patients with atrial fibrillation were taken from a UK general practice database and a nested case-control study was undertaken, which showed that those who developed OA were more likely to be warfarin users than controls. Warfarin users were 59% more likely to develop OA than DOAC users. These studies highlight vitamin K deficiency and inhibition as potential modifiable risk factors for OA. A case could be made for vitamin K supplementation, especially in those with low vitamin K levels, and for use of DOACs in place of warfarin in those at risk of developing OA, or who have established OA.

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