Rheumatology RESEARCH REVIEW™

Making Education Easy

Issue 1 – 2020

In this issue:

Abbreviations used in this issue

COVID-19 = coronavirus disease 2019
CV = cardiovascular
DAS = Disease Activity Score
DMARD = disease-modifying antirheumatic drug
GI = gastrointestinal
HR = hazard ratio
NSAID = nonsteroidal anti-inflammatory drug
RA = rheumatoid arthritis
RCT = randomised controlled trial
RR = relative risk
SARS-CoV-2 = severe acute respiratory syndrome coronaviruses
SLE = systemic lupus erythematosus
TNF = tumour necrosis factor

Welcome to the latest issue of Rheumatology Research Review.

This issue begins with research reporting on adverse events associated with low-dose methotrexate, which is the most commonly used drug for rheumatic diseases and is the recommended first-line treatment for RA. There is also a meta-analysis of adverse events associated with colchicine use, another agent that is widely used for the treatment of inflammatory diseases. We have also included three papers in this issue focussing on COVID-19: one reports specifically on the use of chloroquine and hydroxychloroquine for the treatment of COVID-19, another considers the effects of drugs commonly used to treat RA in the context of COVID-19 and the third reports on the clinical course of COVID-19 in rheumatology patients receiving targeted immunosuppressive therapies. This issue concludes with cost-effectiveness and cost-utility analyses of the TACIT trial, indicating that starting treatment with conventional synthetic DMARDs achieves similar outcomes compared with TNF inhibitors with lower costs.

We hope you enjoy this update in rheumatology research. We would be delighted to receive your comments and feedback.

Kind regards,

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Adverse effects of low-dose methotrexate

Authors: Solomon DH et al.

Summary: Adults with known CV disease and diabetes or metabolic syndrome, who tolerated methotrexate <20mg per week during an active run-in period, were randomised to continue low-dose methotrexate (n=2391) or receive placebo (n=2395); both groups also received folic acid 1 mg/day for 6 days each week. Compared with placebo recipients, a greater proportion of low-dose methotrexate recipients experienced an adverse event of interest (87.0% vs. 81.5%; HR 1.17 [95% CI 1.10, 1.25]), with increased risks of GI events (1.91 [1.75, 2.10]), pulmonary events (1.52 [1.16, 1.98]), infections (1.15 [1.01, 1.30]) and haematological events (1.15 [1.07, 1.23]) and a lower risk of renal adverse events (0.85 [0.78, 0.93]). Low-dose methotrexate did not increase the risk of mucocutaneous, neuropsychiatric or musculoskeletal adverse events or of cancer, except for skin cancer (HR 2.05 [95% CI 1.28, 3.28]).

Comment (SS): Low-dose methotrexate is the first-line treatment for RA and its widespread use has seen it increasingly used in other rheumatic diseases, such as giant cell arteritis and SLE. Methotrexate was adopted as a therapy, without the benefit of large RCTs, following observed improvements in patients treated for haematological malignancies. The first RCT to demonstrate efficacy is usually cited as the noninferiority study between methotrexate and leflunomide in the 1990s. As it would be unethical to compare methotrexate with placebo in RA, the ability to investigate the adverse effects of methotrexate in RA has not been possible in an RCT. A range of adverse effects are widely recognised, and broad consensus exists for monitoring for those most commonly identified.

The current study was able to investigate adverse effects for low-dose methotrexate, used in a placebo-controlled trial – the abandoned Cardiovascular Inflammation Reduction Trial – outside the usual indications. This provides some fascinating data, but with the major caveat that the study group had a very different demographic to a typical RA cohort: 81% male, mean age 65 years, mean body mass index 31 kg/m^2, and all participants had metabolic syndrome or diabetes. Firstly, the overall tolerability of methotrexate was good, with similar overall dosing levels of methotrexate to placebo and mean duration of treatment of 2 years. The overall HR of adverse events for methotrexate versus placebo was only 1.17. In specific areas, the following HRs were of particular interest. Infections: bone and joint 1.9, pneumonia 1.28, ear, nose and throat, and dental 1.2, urinary tract infection 1.3 and shingles 1.34. Respiratory: pneumonitis 6.94 and bronchitis 1.6. GI: nausea/vomiting/diarrhoea 1.3; abdominal pain 1.23, abnormal liver function tests 2.14, nonalcoholic fatty liver disease 1.13, cirrhosis 1.83, anaemia 1.36 and leucopenia 1.46. Cancer: any type 1.13, skin 2.04, bladder 1.39, lung 1.24 and haematological 0.85; skin cancers were predominantly squamous cell carcinomas. Many of these HRs are not surprising and often seen in RA patients during monitoring. If anything, the incidence of nausea and diarrhoea was lower than might be expected in practice. Nonalcoholic fatty liver disease and cirrhosis could be skewed in the population under study, but is an important reminder to monitor patients. A small increased risk of bladder cancer also has implications for screening. Haematological malignancies were lower in the methotrexate group, an important reassurance, as this is sometimes assumed by non-rheumatologists to be a risk of treatment with methotrexate.

In summary, this is an important study highlighting the potential risks of long-term methotrexate therapy, but in all it is mostly reassuring, demonstrating good tolerability and an overall low rate of adverse effects.

Reference: Ann Intern Med 2020;172:369–80
Abstract

Treatment modalities and drug survival in a systemic sclerosis real-life patient cohort

Authors: Panopoulos S et al.

Summary: Current treatment modalities and drug survival rates were reported for a real-world cohort of 497 consecutive patients being treated for systemic sclerosis during 2016–2018. The most frequently used immunosuppressive/antiproliferative agent was methotrexate (53% of patients), followed by cyclophosphamide (26%), mycophenolate mofetil (12%) and azathioprine (11%). For vasoactive agents, calcium-channel blocker, endothelin receptor antagonist, iloprost and sildenafil ever-use was documented for 68%, 38%, 7% and 7% of patients, respectively. Among patients with pulmonary fibrosis, 23% had never received an immunosuppressant or antiproliferative agent, 33% of patients with digital ulcers had never received an endothelin receptor antagonist, iloprost or sildenafil, and 19% of all patients had never received either an immunosuppressant or an antiproliferative agent other than calcium-channel blocker vasoactive agents. Drug survival rates associated with methotrexate, cyclophosphamide and mycophenolate mofetil differed significantly (84%, 59% and 74% at 12 months, respectively, and 75%, 43% and 63% at 24 months), with inefficacy given as the main reason for discontinuation, whereas the rates for calcium-channel blockers, endothelin receptor antagonists and sildenafil were high and comparable (97%, 88% and 80% at 12 months and 91%, 86% and 80% at 24 months).

Comment (SS): Treatment options for systemic sclerosis are generally unsatisfactory, with the exception of vasoactive agents, which have improved morbidity and survival in some patients. Immunomodulatory therapy is poorly supported by small and equivocal studies.

This paper examined the retention of different drugs and classes commonly used to treat systemic sclerosis, which is a novel way of addressing potential benefit. Overall, retention of immunomodulatory therapies was poor. Unfortunately, the study does not provide the indication for starting these, beyond having limited or diffuse systemic sclerosis. Diffuse patients were more likely to be receiving cyclophosphamide, rituximab or mycophenolate mofetil, which may indicate these were being used predominantly to treat pulmonary interstitial fibrosis. Retention was best with methotrexate, with 72% still receiving this drug at 3 years, with adverse events (30%) and disease stabilisation (21%) being the main reasons to discontinue. Vasoactive medications had much higher retention rates between 80% and 95% in the first year. Adverse effects were common, however, affecting up to 70% on endothelin receptor antagonists.

The authors conclude that vascular disease is better managed than immunomodulation, but acknowledge that the risk-benefit ratio for the use of immunomodulatory therapy is often marginal, and some patients may have worsened quality of life on these drugs, without survival benefit. As concluded by the authors, novel agents and rigorous large-scale studies of existing therapies are badly needed in systemic sclerosis.

Reference: Arthritis Res Ther 2020;22:56
Abstract

Adverse events during oral colchicine use

Authors: Stewart S et al.

Summary: This meta-analysis included RCTs of colchicine (n=4225) versus placebo (35 trials; n=3956) or active comparators (five trials; n=411). Compared with comparators, colchicine use was associated with higher rates of diarrhoea (17.9% vs. 13.1%; RR 2.4 [95% CI 1.6, 3.7]) and any GI event (17.6% vs. 13.1%; 1.7 [1.3, 2.3]), but was not associated with significantly increased rates of liver, sensory, muscle, infectious or haematological adverse events or death.

Comment (SS): Colchicine has had a modest renaissance since the toxic loading regimen promoted in the twentieth century was abandoned. A recent study has shown comparable rapidity of onset and efficacy to NSAIDs in managing acute gout.

In this systematic review, undertaken in Australia and NZ, adverse effects of colchicine were investigated. In all, 35 studies were identified with a range of indications – only five for gout – and durations and dosage regimens. The RR of an adverse event was 1.46 compared with placebo. The risk of an adverse event was not affected by daily dose regimen, duration of treatment or cumulative dose. Dosages in the studies were between 0.6mg three times daily and 0.5mg daily. The most common adverse event was diarrhoea with an adjusted RR of 2.14. The RR for all GI adverse events was 1.60, and included, nausea, vomiting, bloating, abdominal pain and diarrhoea. Other adverse events associated with colchicine were not significant in this analysis. Muscle adverse events including rhabdomyolysis, raised creatine kinase level, myalgia, myopathy, haematological abnormalities, liver toxicity and sensory neuropathies were nonsignificant.

The above data are reassuring. It seems that not only is colchicine an effective anti-inflammatory in certain disease conditions, but is also a safe one if used at standard low therapeutic dosages. Whilst GI adverse events certainly limit its use in some patients, these are not usually serious and resolve rapidly with cessation of treatment.

Reference: Arthritis Res Ther 2020;22:28
Abstract

Withdrawal of low-dose prednisone in SLE patients with a clinically quiescent disease for more than 1 year

Authors: Mathian A et al.

Summary: Patients receiving prednisone 5 mg/day for SLE that was clinically inactive were randomised to continue (n=61) or stop (n=63) this treatment. Compared with participants who stopped prednisone, those who continued the agent were at lower risk of disease flare (RR 0.2 [95% CI 0.1, 0.7]), including mild/moderate and moderate/severe flares (0.2 [0.1, 0.8] and 0.1 [0.1, 0.9], respectively), and had a shorter time to first flare (HR 0.2 [0.1, 0.6]). There was no significant between-group difference for increase in Systemic Lupus International Collaborating Clinics damage index score or adverse events.

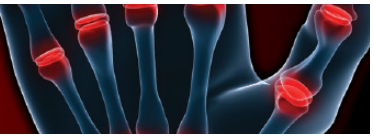
Comment (SS): The long-term management of SLE is challenging. Many patients with SLE remain on low-dose prednisone, but whether this is helpful or associated with harm is uncertain. This small study, over a relatively short 12-month follow-up, examined this by abruptly stopping prednisone in a group of patients and maintaining low-dose prednisone 5mg daily in another group (allocated 1:1). Assessments of flare and disease activity were made over this period and assessments were performed by blinded adjudicators. There was no control group and the patients were not blinded to the intervention. The patients had a range of historical disease severity and about one in four were taking an immunosuppressant (methotrexate, azathioprine, mycophenolate mofetil). Patients who stopped prednisone had a cumulative increase in flares over the 12-month period, with the greatest rate of increase between 100 and 200 days postcessation (p=0.002). This equated to a 27% relapse rate in the withdrawal group. Arthritis and skin manifestations seemed most common.

This study has a number of risks of bias. Firstly the patients were not blinded to the intervention and may have reported symptoms more readily knowing they were in the withdrawal group. Secondly, there may have been inclusion bias with only patients already receiving long-term prednisone included. Withdrawal of prednisone was also very rapid and did not reflect usual clinical practice. Although the findings of this study are in many ways unsurprising, as flares when stopping prednisone are a common experience, they do not make a strong case for continuing prednisone indefinitely, because of the many flaws in its design and the small sample size. The risks and benefits of prednisone need to be evaluated on an individual basis.

Reference: Ann Rheum Dis 2020;79:339–46
Abstract

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.



Chloroquine and hydroxychloroquine in COVID-19

Authors: Ferner RE & Aronson JK

Summary: This article discussed the use of chloroquine and hydroxychloroquine for the treatment of COVID-19. The authors discussed relevant historical information regarding the potential for these agents to have antiviral activity, in the context of such use being premature and possibly harmful. They also summarised data from laboratory studies, and highlighted the inadequacies in the methodologies and reporting of studies claiming benefit with these agents in COVID-19. They concluded that better, adequately powered RCTs are needed.

Comment (SS): Rheumatologists and patients have become concerned about the potential for shortages in supply of hydroxychloroquine, following the widespread publicity regarding its possible efficacy in treating COVID-19, especially fuelled by President Donald Trump's advocacy based on political expediency. But what is the existing level of evidence and why has it been seized upon? This article provides some good background for the rheumatologist. Hydroxychloroquine is a 4-aminoquinoline, a group of drugs known to be active *in vitro* against a range of viruses. In SARS-CoV-2, hydroxychloroquine inhibits glycosylation of angiotensin converting enzyme-2, the receptor that SARS-CoV-2 uses to enter cells in the respiratory tract. This laboratory-based finding has led to open-label trials (prematurely) reported, and to the registering of at least 80 clinical trials of chloroquine, hydroxychloroquine or both, some combined with other drugs. A recent French study from a well-respected group has been particularly controversial, resulting in much scientific and media disdain. This open, nonrandomised study of hydroxychloroquine suggested efficacy in 20 patients, but six patients dropped out of the treatment arm, two due to admission to ICU, and one died, and the measure of efficacy was viral load, not a clinical response.

Concern regarding the (short-term) toxicity of hydroxychloroquine will seem baffling to rheumatologists, who usually see it as the most benign drug in their armamentarium. Perhaps a more pernicious effect of this hype and furore is that combined therapy with hydroxychloroquine and azithromycin seems to be associated with prolonged QT syndrome and fatal arrhythmias in some patients with COVID-19. This is not seen in standard doses used in rheumatic disease, but a push for ECG monitoring in our patients could be a negative result of this attention. There is an urgent need for effective antiviral agents to treat COVID-19. Whether hydroxychloroquine will prove useful, alone or in combination, remains to be seen. Perhaps one or more of the 80 trials initiated will provide the answer. In the meantime, Pharmac has acted promptly and ethically to restrict the use of this drug to those already receiving it, or prescribed appropriately for a registered indication.

Reference: BMJ 2020;369:m1432
Abstract

COVID-19 infection and rheumatoid arthritis: faraway, so close!

Authors: Favalli EG et al.

Summary: These authors reviewed the pathophysiology of COVID-19 infection and discussed the increased risk of viral infections in patients with RA. They presented current information on the effects that drugs used for rheumatic diseases have on viral infections, including corticosteroids, NSAIDs and conventional synthetic, biological and targeted synthetic DMARDs. They also considered the spectrum of antirheumatic drugs in the management of COVID-19; they included a table listing the pros and cons for the various classes/agents, including chloroquine/hydroxychloroquine, IL-1 and IL-6 antagonists, TNF inhibitors and Janus kinase inhibitors.

Comment (AH): This is a rapidly evolving area of investigation, and any publication is at risk of being rendered obsolete by the emergence of new data, but as of this moment, this review provides a reasonable summary of existing knowledge concerning the management of RA during the COVID-19 pandemic. The key message is that RA patients are at increased risk of infection, primarily due to the disease itself, with a further contribution from some treatments – specifically corticosteroids and biological therapies, although not, as is commonly assumed, from use of oral disease-modifying drugs. There is evidence that risk of hospitalisation with infection correlates with disease activity, so maintaining good disease control may be protective. This reinforces the message that patients should continue treatment during the pandemic. The review concludes by speculating that treatments for RA may be protective, including hydroxychloroquine (for which the *in vitro* evidence shows promise but the clinical evidence is not strong), IL-6 inhibitors (for which there is emerging evidence) and TNF-inhibitors (for which a trial of adalimumab is underway).

Reference: Autoimmun Rev 2020;19:102523
Abstract

Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies

Authors: Monti S et al.

Summary: These authors reported the results of a survey with 2-week follow-up contact of 320 outpatients with RA (57%) or spondyloarthritis (43%) treated with TNF inhibitors (52%), other biological DMARDs (40%) or targeted synthetic DMARDs (8%) during the COVID-19 outbreak in the Lombardy region of Italy. There were four patients with confirmed COVID-19, four with highly suggestive COVID-19 symptoms and five asymptomatic patients who reported contact with COVID-19 cases. The investigations did not allow any conclusions to be drawn regarding the incidence of SARS-CoV-2 infection in patients with rheumatic diseases or the outcomes of immunocompromised patients with COVID-19.

Comment (AH): This study comes from Lombardy, the epicentre of the COVID-19 outbreak in Northern Italy. The authors received survey responses from 320 patients under the surveillance of a biologics clinic who were taking biological DMARDs or targeted synthetic DMARDs (tofacitinib or baricitinib) for various rheumatological conditions. There were four confirmed cases of COVID-19 and four probable cases, with a further five who had contact with a known COVID-19 patient, none of whom became symptomatic. Of the confirmed and probable cases, only one was admitted to hospital for a few days of low-flow oxygen treatment plus antiviral therapy and hydroxychloroquine. All cases withheld biological DMARDs and targeted synthetic DMARDs while they were symptomatic and all patients made a complete recovery. Although the small size of the study population does not allow any conclusions to be reached, the low number of cases, the good outcomes and the fact that contact with known cases did not inevitably result in infection does at least provide some reassurance that even the most technologically advanced treatments for rheumatic disease do not seem to increase infection risk in people with rheumatic disease.

Reference: Ann Rheum Dis 2020;79:667–8
Abstract

Trends in all-cause and cardiovascular mortality in patients with incident rheumatoid arthritis

Authors: Provan SA et al.

Summary: All-cause and CV disease-related mortality outcomes were compared between consecutive patient cohorts with incident RA from the Oslo RA register versus population comparators during three time periods in this study with 20 years' follow-up; 443, 479 and 469 patients with incident RA during the respective 1994–1998, 1999–2003 and 2004–2008 periods were matched to 4430, 4790 and 4690 controls. There was significant divergence for all-cause mortality of cases versus controls after 10 years of disease duration for the 1994–1998 and 1999–2003 cohorts (respective HRs 1.42 [95% CI 1.15, 1.75] and 1.37 [1.08, 1.73]), and CV disease-related mortality was significantly increased after 5 years in the 1994–1998 cohort (1.86 [1.16, 2.98]) and after 10 years in the 1999–2003 cohort (1.80 [1.20, 2.70]). There was no increased mortality in the 2004–2008 cohort; 10-year all-cause and CV disease-related mortality rates among cases were significantly lower compared with earlier cohorts.

Comment (AH): The key findings in this study were that all-cause mortality and CV-related mortality were less in the cohort diagnosed after 2004 than in the earlier cohort. Whereas all-cause and CV-related mortality diverged from non-RA controls in the earlier cohort, the disparity had vanished in the post-2004 cohort. Reasons for this are speculative, but likely to be due to better control of systemic inflammation, which is associated with increased risk of CV disease. Risk of serious infection is also correlated with disease activity, and may account for some of the excess mortality in the earlier cohort that is not explained by CV causes of death. The life-saving effects of good control of inflammation should be included in any cost-benefit and risk-benefit analysis of DMARD therapy in RA.

Reference: Rheumatology 2020;59:505–12
Abstract

Is treat-to-target really working in rheumatoid arthritis?

Authors: Ramiro S et al

Summary: These researchers analysed disease activity over 2 years in 571 patients with RA who attended 4356 daily-practice visits and started or changed conventional synthetic or biological DMARD therapy; appropriate application of a treat-to-target strategy was evident at 59% of the visits. Treat-to-target was not associated with a greater likelihood of remission at 3 months according to DAS44 (44-joint Disease Activity Score; odds ratio 1.03 [95% CI 0.92, 1.16]), but a sustained treat-to-target strategy did increase the likelihood of achieving DAS44 remission (1.19 [1.03, 1.39]); the results were similar when remission was defined by the DAS28-ESR (28-joint DAS-erythrocyte sedimentation rate). Treat-to-target was consistently associated with remission defined by CDAI (Clinical Disease Activity Index), SDAI (Simplified Disease Activity Index) and ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) Boolean criteria (odds ratios 1.16–1.29, increasing to 1.49–1.52 with a sustained treat-to-target strategy).

Comment (AH): This study sought to determine whether the treat-to-target strategy of increasing treatment when remission has not been achieved and leaving treatment unchanged when the target has been reached would lead to higher rates of remission compared with cases in which this strategy was not correctly applied. Using data from the RA BIODAM cohort, 571 patients with RA were followed. Patients in whom treat-to-target was applied were significantly more likely to have achieved ACR/EULAR Boolean, CDAI and SDAI remission or low disease activity 3 months later, whether or not corticosteroids were used, and patients for whom treat-to-target was sustained over the course of the study also had significantly higher rates of sustaining DAS44, DAS28-ESR, ACR/EULAR Boolean, CDAI and SDAI remission. This study shows that a treat-to-target approach in RA can lead to better control of disease activity.

Reference: Ann Rheum Dis 2020;79:453–9
Abstract

Cost-effectiveness of combination disease-modifying antirheumatic drugs versus tumor necrosis factor inhibitors in active rheumatoid arthritis

Authors: Patel A et al.

Summary: Patients from England and Wales with RA were randomly allocated to receive conventional synthetic DMARDs (n=104) or TNF inhibitors (n=101) in this open-label, 12-month, pragmatic, noninferiority trial with cost-effectiveness and cost-utility analyses from healthcare and social care and two societal perspectives; participants in the conventional synthetic DMARD arm who had a poor response at 6 months could switch to TNF inhibitor therapy, and 46 did so. Relevant 6- and 12-month cost and outcome data were available for 93% and 91–92% of participants, respectively. Compared with TNF inhibitor recipients, conventional synthetic DMARD recipients accrued significantly lower total costs from all perspectives; the respective adjusted mean differences in 6- and 12-month health and social care costs were –£3615 and –£1930. Conventional synthetic DMARD recipients also had better Health Assessment Questionnaire scores at 12 months, but there was no significant between-group difference for quality-adjusted-life years.

Comment (AH): The TACIT trial was an open-label study that compared responses to two strategies for treatment of early RA (<12 months' duration): conventional synthetic DMARDs versus a TNF inhibitor, the choice being determined by local practice, and conventional synthetic DMARDs being added sequentially as needed. After 12 months, conventional synthetic DMARDs were noninferior to TNF-inhibitors. Here the TACIT investigators report on the cost-benefit analysis, which was determined from prospectively recorded data. Costs included lost pay and social security benefits, and the only costs that differed between the two groups were drug costs, which were significantly higher in the TNF inhibitor arm: £3615 greater at 6 months and £1930 at 12 months. This study supports the use of conventional synthetic DMARDs as first-line treatments in RA. It does not undermine the cost effectiveness of TNF inhibitors for the treatment of patients who have failed treatment with conventional synthetic DMARDs, for whom the costs of morbidity and mortality, personal economic costs, social isolation and loss of quality of life are enormous.

Reference: Arthritis Care Res 2020;72:334–42
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. **FOR FULL BIO CLICK HERE**