Rheumatology Research Review™

Making Education Easy

Issue 141 - 2022

In this issue:

Abbreviations used in this issue:

AME = adverse medical experience
AOSD = adult-onset Still's disease
AUSCAN = Australian/Canadian Osteoarthritis Hand Index
BMI = body mass index
DAS = disease activity score
HA = hyaluronic acid
HC = high-carbohydrate
IED = inflammatory eye disease
KOOS = Knee Injury and Osteoarthritis Outcome Score
LF = low-fat
MD = Mediterranean diet
mSFS = modified Systemic Feature Score
NRS = Numerical Rating Scale
OA = osteoarthritis
RA = rheumatoid arthritis
RR = relative risk
SLE = systemic lupus erythematosus
WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

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Welcome to the 141st issue of Rheumatology Research Review.

A 12-year cohort study included in this issue reports inflammatory eye disease was associated with rheumatologic disease development. Another cohort study investigated the use of low-dose oral glucocorticoids and risk of osteoporotic fractures among patients with rheumatoid arthritis. The authors suggest clinicians should be aware that even in patients who receive low daily glucocorticoids, the risk of clinical vertebral fracture is increased. Researchers using data from a genome-wide association study found polygenic risk scores are associated with the level of severity of radiographic progression in rheumatoid arthritis.

There are also a number of articles in this issue with a focus on osteoarthritis. A prospective, randomised controlled trial found repeated co-injections of corticosteroids plus hyaluronic acid more effectively decreased pain and improved physical function than injections of hyaluronic acid alone. A cluster-randomised trial found no effect of duloxetine added to usual care compared to usual care alone in patients with chronic knee or hip osteoarthritis pain. The concluding article is fascinating research exploring medication decision-making and adherence in lupus. The findings highlight the persisting negative effect of adverse medical experiences, which include being disbelieved or dismissed about one's symptoms or fearing your doctor's lack of knowledge.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards

Associate Professor Les Barnsley
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Dietary pattern or weight loss: Which one is more important to reduce disease activity score in patients with rheumatoid arthritis? A randomized feeding trial

Authors: Sadeghi A, et al

Summary: Overweight and obese patients with rheumatoid arthritis (RA) were randomised to Mediterranean diet (n=51) and low-fat (LF) high-carbohydrate (HC) diet (n=53) for 12 weeks. The control group followed their regular diet (n=50). Participants completed the form of tender and swollen joint counts at baseline and after 12 weeks to calculate disease activity score 28 (DAS 28). The researchers reported weight loss was not statistically significant between the MD and LF-HC groups. DAS 28 significantly decreased in MD compared to the LF-HC group (p=0.02) and controls (p=0.001). Adjusting for the baseline variables, MD reduced DAS 28 by 76% (95% CI=−0.45, −0.2; p=0.03) after 12 weeks of intervention. They noted baseline serum ESR level showed 99.8% effect on DAS 28 score (95% CI=0.014, 0.035; p<0.001).

Comment: Many of my RA patients tell me that they are following an "anti-inflammatory" diet. My response is usually to encourage them to try to achieve ideal body weight and consume lots of fish as I extol the proven virtues of fish oil. I am not sure how palatable my patients find these rather superficial suggestions. The discussions become more complicated when other factors, such as vegetarianism and religious dietary observances, are added to the mix. Hungry for more information I considered this study. The design is reasonably straightforward, but there were a few things that concerned me. The control group (usual diet) had lower BMI than the LF-HC or MD groups. Only those who were >80% compliant with their diet were eligible for the final analysis, and the consort diagram suggests this was everybody who was randomised, which I find hard to swallow. The MD was interesting, allowing only 150g red meat per month. For the most part it was vegetables, nuts, olive and canola oils plus fish oil supplements. Both active diet groups lost weight, but the MD diet patients achieved lower ESRs and DAS 28 ESR scores. Given the other health advantages of Mediterranean diets, I think this study, even with its flaws, provides useful information.

Reference: Intern J Clin Pract. 2022 Apr. Article ID 6004916

Abstract

No added value of duloxetine in patients with chronic pain due to hip or knee osteoarthritis: A cluster-randomized trial

Authors: van den Driest JJ, et al

Summary: The open-label trial assessed the effectiveness of duloxetine in patients with chronic osteoarthritis (OA) pain who had an insufficient response to acetaminophen and nonsteroidal antiinflammatory drugs. Patients were randomised to receive duloxetine (60mg/day) in addition to usual care (n=66), or usual care alone (n=66). The presence of centralised pain was defined as a modified PainDETECT Questionnaire score >12. The primary outcome measure was Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores at 3 months. The investigators found no differences in WOMAC pain scores between the groups at 3 months (adjusted difference -0.58) or at 12 months (adjusted difference -0.26). In the subgroup of patients with centralised pain symptoms, they also found no effect of duloxetine compared to usual care alone (adjusted difference -0.32).

Comment: The idea of using drugs which modulate pain centrally is not new to rheumatologists and duloxetine is well established in the pharmacological treatment of fibromyalgia. Our understanding of pain as a continuum between pure peripheral nociceptive pain and central sensitisation is an important refinement and invites the intervention tested in this study, and currently supported by ACR and OARSI guidelines. The negative results of this study are therefore a bit surprising. The methods therefore deserve closer scrutiny before we accept the findings. The population tested was highly selected, with significant exclusions based on medication use and comorbidities. The study was open with no blinding of participants, GPs or investigators. In general, these study characteristics would be expected to bias the study towards a positive outcome, although a nocebo effect could also be introduced in the control group. Overall, I think the trial argues against an important effect of duloxetine in this patient group. It will be interesting how this influences the next round of guideline development.

Reference: Arthritis Rheumatol. 2022 May;74(5):818-828
Abstract

The incidence, risk factor, and time to develop rheumatologic diseases after isolated inflammatory eye diseases: A 12-year cohort study

Authors: Sumethkul K, et al

Summary: The 12-year bidirectional cohort study was conducted in patients with isolated inflammatory eye diseases (IED) who were tested for antinuclear antibody and rheumatoid factor. Patients with prior rheumatologic disease were excluded. Seventy-five patients presented with IED including scleritis, anterior uveitis, retinal vasculitis, keratopathy and optic neuritis. The authors concluded anterior uveitis, retinal vasculitis, keratopathy, and optic neuritis were associated with rheumatologic disease development. The incidence of rheumatologic disease was 36% during 12 years. Rheumatologic disease developed most frequently in anterior uveitis (55.5%) and retinal vasculitis (22.2%). The longest duration for rheumatologic disease development was 5.5 years. Prevalence of positive antinuclear antibody and rheumatoid factor were 57.3% and 13.3%, respectively. The three most common rheumatologic diseases developed after IEDs were spondyloarthropathy (44.4%), systemic lupus erythematosus (SLE) (18.5%), and Sjogren's syndrome (11.1%). They noted risk factors of rheumatologic disease were age below 35 years old at onset of IED (relative risk (RR) 3.45, p =0.026), positive pertinent findings from history (RR 2.125, p<0.001), and physical examination (RR 3.23, p<0.001). Furthermore, bilateral eye involvement of IED was the most significant risk of rheumatologic disease (RR 4.33, p=0.004).

Comment: We are occasionally asked to assess patients with IED to rule in or rule out systemic rheumatic disease. This Thai study provides some insights to inform that assessment. About a third of patients developed a definable rheumatic disease according to appropriate criteria over the next 12 years, with most in the first 12 months and half having a symptom or sign suggesting a rheumatic condition at the time of IED diagnosis. The most useful predictive factor was bilateral involvement, so we should keep our eyes open for that. Screening with serology was not especially helpful but the high yield from a formal rheumatological assessment was professionally reassuring.

Reference: Clin Rheumatol. 2022 Apr;41(4):1003-1012
Abstract

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Independent commentary by Associate Professor Les Barnsley

Associate Professor Barnsley holds Medicine, Epidemiology and Philosophy degrees. He is a Fellow of the Royal Australasian College of Physicians and a Scientific Fellow of the Faculty of Rehabilitation, Royal Australasian College of Physicians. He is Senior Staff Specialist and Associate Professor in the Department of Medicine at the University of Sydney. Associate Professor Barnsley has contributed chapters to textbooks and has over 60 articles in peer-reviewed journals, including two in the New England Journal of Medicine. He was a member of the Expert Writing Committee for the 1st, 2nd and 3rd editions of Therapeutic Guidelines in Rheumatology. He has been the Principal Investigator in several industry-sponsored trials of therapies for RA and OA. His research interests include spinal pain, whiplash, musculoskeletal medicine, medical education and general rheumatology.

Associated factors with poor treatment response to initial glucocorticoid therapy in patients with adult-onset Still's disease

Authors: Kondo F, et al

Summary: This retrospective cohort study aimed to identify prognostic factors for poor treatment response to initial glucocorticoid therapy for adult-onset Still's disease (AOSD). The primary outcome was a poor treatment outcome at 4 weeks, which was defined as failure to achieve remission or relapse after achieving remission within 4 weeks, followed by administration of two or more rounds of glucocorticoid pulse therapy or of any other immunosuppressive drugs. Of the study cohort of 71 patients 34 (47.3%) received glucocorticoid pulse therapy at week 0. Twenty-nine of 71 (40.8%) patients exhibited a poor treatment outcome at 4 weeks. The second round of glucocorticoid pulse therapy or immunosuppressive drugs was added in 17 or 24 of the 29 patients, respectively. These patients had higher baseline WBC counts, serum ferritin levels, systemic feature score based on clinical symptoms (modified systemic feature score, mSFS), more hemophagocytic syndrome over the 4 weeks, and the higher severity score than the remaining 42 patients. The authors identified baseline WBC count as a prognostic factor for poor outcome (odds ratio per 1000/μl increment: 1.12), while thrombocytopenia, hyperferritinemia, and mSFS at baseline did not achieve statistical significance. They also noted the optimal cut-off for WBC count was 13,050/μl and the cumulative rate of poor treatment outcome to be 60.0% in patients with WBC ≥13,050/μl and 23.5% in those with WBC <13,050/μl.

Comment: Rare conditions present challenges to clinicians as we typically lack extensive personal experience, or risk having our views and decisions swayed by stochastic events. At the same time, when your patient has a rare condition the in-room point prevalence is 50% and the individual is just as deserving of evidence-based therapy as anybody else. I therefore appreciate the publication of studies such as this, which attempts to identify characteristics of AOSD patients which portend a poor response to steroids. I think the design was the best you can reasonably expect for such an unusual condition, being a retrospective chart review. The key finding was that a white cell count over 13,000/μl was strongly associated with poor response to treatment. This may help us initiate earlier additional immunosuppressives in patients at risk of relapse.

Reference: Arthritis Res Ther. 2022 Apr 29;24(1):92
Abstract

Association of polygenic risk scores with radiographic progression in patients with rheumatoid arthritis

Authors: Honda S, et al

Summary: The investigators constructed polygenic risk scores using genome-wide association study data on associations of single-nucleotide polymorphisms with RA susceptibility. Polygenic risk scores were assessed for their ability to predict radiographic progression over 5 years in a training set (n=500 RA patients) for selection of the best model, and in a testing set (n=740 RA patients) for validation of the data. The investigators reported polygenic risk scores constructed from 43,784 single-nucleotide polymorphisms significantly differed between patients who experienced severe radiographic progression and those with nonsevere radiographic progression in both the training set (P=0.0064) and the testing set (P=0.017). They also found polygenic risk score (P=0.00019) as well as female sex (P=0.0033), anti-citrullinated protein antibody positivity (P=0.0023), and body mass index (P=0.024) were independent risk factors for severe radiographic progression.

Comment: Gattaca was the cleverly titled film of a world where one's genetic information was scrutinised to predict one's medical future. This study feels as if that future is a little closer. I do not pretend to understand the genetic techniques, but the authors explored the influence of thousands of single nucleotide polymorphisms in RA patients to produce a score called a polygenic risk score. This was incorporated into a model to predict the likelihood of radiographic progression and was independently positively correlated. I suspect that this sort of analysis will become more sophisticated and automated as time progresses. It highlights the value of initiatives such as the A3BC (Australian Arthritis and Autoimmune Biobank Collaborative) project in collecting pertinent information to develop predictive models and is one more step towards personalised medicine.

Reference: Arthritis Rheumatol. 2022 May;74(5):791-800
Abstract

Effects of repeated co-injections of corticosteroids and hyaluronic acid on knee osteoarthritis: A prospective, double-blind randomized controlled trial

Authors: Wang CP, et al

Summary: Patients with clinical and radiographic knee osteoarthritis were assigned to either the hyaluronic acid (HA) group (n=29) or corticosteroids plus HA group (n=28). Injections were administered under ultrasound guidance once a week for 3 consecutive weeks. WOMAC scores were the primary outcomes and physical functional performance (10-m fast walking and chair-rising time) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) were secondary outcomes. The assessment was performed prior to injections, 1 week, and 1, 3, and 6 months after injections. The authors reported both groups experienced decreased pain and improved physical function and physical functional performance over time. They found significant group × time interaction effects favouring the corticosteroids plus HA group in WOMAC-pain (P=0.005) and physical function (P=0.005), chair-rising time (P=0.032), and KOOS-pain (P=0.001).

Comment: At first glance, this small trial looks quite straightforward. The combination of HA with corticosteroid injection works better than HA alone for appropriate outcome measures. However, the intervention was three, weekly injections of HA plus or minus 10mg of triamcinolone, which would be an unusual regimen for steroid if it were used alone. A steroid only group with this dose may have given us more information. I don't think this will change my practice at this stage.

Reference: Am J Med. 2022 May;135(5):641-649
Abstract

Low-dose oral glucocorticoid therapy and risk of osteoporotic fractures in patients with rheumatoid arthritis: A cohort study using the Clinical Practice Research Datalink

Authors: Abtahi S, et al

Summary: Among the study cohort of 15,123 patients with RA 1,640 osteoporotic fractures occurred. Exposure to oral glucocorticoids was stratified by the most recent prescription in current (<6 months), recent (7-12 months) and past (>1 year) use, and average daily and cumulative doses. The researchers showed current low-dose oral glucocorticoid therapy (≤7.5mg prednisolone equivalent dose/day) in patients with RA was not associated with overall risk of osteoporotic fractures (adjusted HR 1.14, 95% CI 0.98, 1.33) compared with past glucocorticoid use, but was associated with an increased risk of clinical vertebral fracture (adjusted HR 1.59, 95% CI 1.11, 2.29). Results remained unchanged regardless of a short-term or a long-term use of oral glucocorticoids.

Comment: The judicious use of corticosteroids is still a part of RA management and is supported by EULAR guidelines. I had thought of lower doses, say less than 7.5mg/day as reasonably safe, but this trial adds to other data that makes me increasingly uncomfortable with that assumption. The investigators tried to minimise effects such as confounding by indication or disease severity, which is the main risk of bias in this type of retrospective study, where steroid-treated patients are sicker, or have more severe disease so they are more likely to have fractures for other reasons. However, they did not have access to which patients were on biologics and there was no direct data on disease severity. They found that at doses below 7.5mg, there was an increased risk of clinical vertebral osteoporotic fractures, but not at other sites. My take on this is that trying to keep your RA patients off corticosteroids is a good thing, but I think I knew that anyway.

Reference: Rheumatology (Oxford). 2022 Apr 11;61(4):1448-1458
Abstract

Associations of body mass index with pain and the mediating role of inflammatory biomarkers in people with hand osteoarthritis

Authors: Gløersen M, et al

Summary: The researchers estimated associations between BMI and hand pain in 281 people with hand OA, as measured by the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) and Numerical Rating Scale (NRS); foot pain, as measured by NRS; knee/hip pain, as measured by the WOMAC; painful total body joint count; and pain sensitisation. They reported each 5-unit increase in BMI was associated with more severe hand pain (on average increased AUSCAN by 0.64), foot pain (on average increased NRS by 0.65), knee/hip pain (on average increased WOMAC by 1.31), generalised pain, and pain sensitisation. Mediation analyses suggested that the effects of BMI on hand pain and painful total body joint count were partially mediated by leptin and high-sensitivity C-reactive protein, respectively. They noted effect sizes for mediation by leptin were larger for the hands than for the lower extremities and were statistically significant for the hands only.

Comment: Osteoarthritis remains a frustrating condition for both patient and doctor. It is painful and disabling. The link between lower limb OA and obesity is well established and has face validity. This study supports other studies that found a link between obesity and hand OA, specifically the degree of pain. The authors try to tease out the contribution of leptin and proinflammatory cytokines found at higher levels in obese individuals. The key issue to me is whether weight loss will favourably influence extant hand OA pain. At the same time, the abundant health benefits of weight loss make it something of a moot point. Perhaps we can borrow from the language of vitamin marketers. "Weight loss may help support hand pain in medically diagnosed osteoarthritis".

Reference: Arthritis Rheumatol. 2022 May;74(5):810-817
Abstract

Medication decision-making and adherence in lupus: Patient-physician discordance and the impact of previous 'adverse medical experiences'

Authors: Sloan M, et al

Summary: The authors used in-depth interviews (n=23) and quantitative survey findings (n=186) to explore the impact of current and previous medical experiences on patient satisfaction and medication adherence. They identified five themes: (i) physician-patient discordance and a 'hierarchy of evidence' in medication decisions; (ii) the association of adherence with satisfaction with care; (iii) the persisting impact of past adverse medical experiences (AMEs); (iv) the dynamic balance of patient-physician control; and (v) holistic care, beyond a purely medication-based focus. The importance of listening to patients was a key component of every theme and associated with patient satisfaction and adherence. It was noted the main reasons for adherence were improving quality of life (43% of participants) and a supportive medical relationship (24%). Patients with past AMEs had statistically significant lower satisfaction with care.

Comment: This is a genuinely fascinating piece of work. It used a questionnaire to explore several issues around medical consultations and medication adherence then performed some semi-structured qualitative interviews to determine the themes underpinning the answers. A highlight to me was the persisting negative effect of AMEs which included being disbelieved or dismissed about one's symptoms or fearing your doctor's lack of knowledge. Other key findings were the positive relationship between the patient's assessment of their physician's listening skills, adherence and satisfaction and a discord between what the doctor found important (blood results and preventing organ damage) and patient concerns (symptom control and quality of life). The study selected patients from a systemic lupus erythematosus (SLE) forum and an SLE Facebook group, so may have included those with more difficult disease or with particular concerns. However, I don't think we can disregard these important insights on that basis.

Reference: Rheumatology (Oxford). 2022 Apr 11;61(4):1417-1429
Abstract