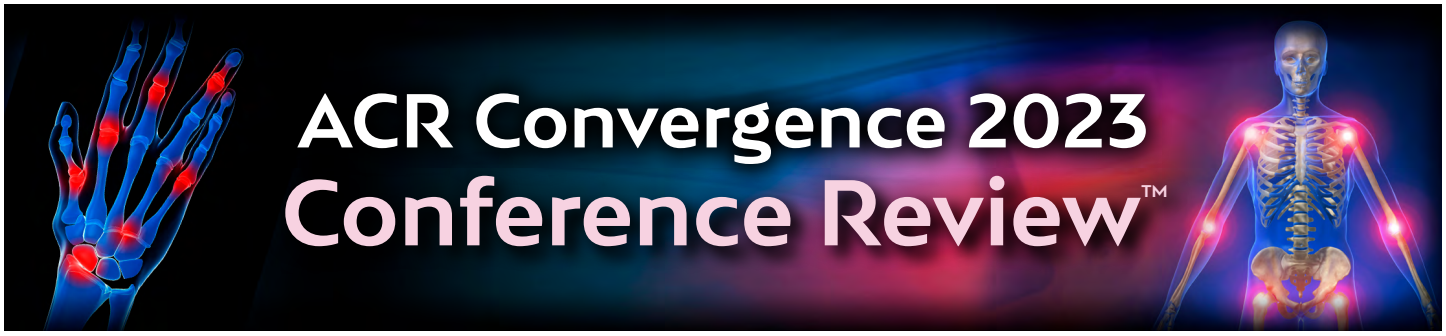

Making Education Easy

San Diego Convention Centre, California, Nov 10-15, 2023

In this review:

Abbreviations used in this review:

HR = hazard ratio; **ILD** = interstitial lung disease; **LBP** = lower back pain; **MTX** = methotrexate; **OA** = osteoarthritis; **PMR** = polymyalgia rheumatica; **RA** = rheumatoid arthritis; **TKR** =total knee replacement; **TNF** = tumour necrosis factor.

Welcome to this review of the American College of Rheumatology (ACR) Convergence 2023,

held in San Diego, California. This year's programme showcased cutting-edge and timely topics in rheumatology and focused on the prevention, treatment and diagnosis of rheumatic diseases and other related comorbid conditions. The global learning objectives highlighted in this year's meeting included the identification of recent developments in the diagnosis and management of patients with rheumatic diseases, outlining the use of new technologies and treatments for rheumatic problems, describing the potential challenges in the delivery of patient care and utilisation of new research data to improve the quality and delivery of care to patients with rheumatic diseases, as well as summarising the recent and emerging findings in rheumatic research.

We hope you enjoy the comments provided in this review of the ACR convergence. As always, we look forward to receiving your feedback.

Kind Regards,

Professor Peter Youssef
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Leukotriene inhibitors effect on post-traumatic osteoarthritis

Authors: Jafarzadeh SR et al.

Summary: This real-world study, conducted between 2006 and 2020, focused on individuals undergoing ACL or meniscal surgery, drawn from the MarketScan Commercial Claims and Encounters databases. The analysis included 13,800 participants, predominantly female (50%), with a mean age of 35.4 years. The research compared the odds of total knee replacement (TKR) and osteoarthritis (OA) outcomes between users of leukotriene inhibitors and long-acting beta-agonists post-surgery. Results revealed that after adjusting for confounders, leukotriene inhibitor users exhibited a 4% lower odds of TKR at five years and an 11% lower odds at ten years compared to beta-agonist users.

Comment: Reducing post-traumatic OA after meniscal or ACL surgery is one of the holy grails of OA treatment. Despite the limitations of studies using large claims commercial databases, this study tantalisingly shows a reduction in TKR in patients using leukotriene antagonists compared with beta-agonists, presumably because inhibiting mast cell activation reduces inflammation and the development of OA. It may be worth doing prospective long-term studies as the cost saving to the community would be significant because there appeared to be a reduction in TKR as early as five years post-injury.

Reference: 0147
Abstract

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Independent commentary by Professor Peter Youssef

Professor Peter Youssef 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.

Impacts of social determinants of health and the immune system in adults with acute-to-chronic low back pain

Authors: Burke C et al.

Summary: This study involved 26 adults with acute low back pain (LBP) for less than 4 weeks and aimed to explore the association between social factors and immune responses. Social roles were found to have the strongest link to immune cell changes and plasma cytokines. Confidence in upholding social roles was associated with lower inflammatory cytokines and TNF expression but higher CD8 T cell proliferation. In terms of race, White participants exhibited higher inflammatory cytokines, and immune cell differences between Black and White participants were observed. Individuals not transitioning to chronic LBP showed weaker immune responses, suggesting a possible immune tolerance or desensitisation in those who did not progress to chronic LBP.

Comment: Back pain remains a major clinical problem. The biopsychosocial model is well accepted in medicine, and this interesting poster dips its toes into exploring how social determinants may alter pro-inflammatory cytokines and influence the progression of patients from acute back pain to chronic back pain. Not surprisingly, confidence in the ability to uphold social roles was associated with reduced inflammation. The move towards precision medicine dictates that we will be seeing more of these studies as we try and tailor treatment to biology. We may eventually discover treatments that are effective for chronic back pain.

Reference: 0149
Abstract

Gout: A gateway to chronic opioid use?

Authors: Helget L et al.

Summary: In this matched cohort study utilising national VHA data from 1999 to 2015, patients with gout were identified based on ICD-9 codes and compared to those without gout. The study followed individuals from the index date until the earliest of chronic opioid use initiation, death, or five years post-index. Among 16.7 million patient-years, 6.9% of gout patients initiated chronic opioids, compared to 3.8% of non-gout patients. After adjusting for covariates, gout patients were significantly more likely to start chronic opioids (average HR 1.36). Factors positively associated with gout-related chronic opioid use included the Black/African American race, comorbidities, urate-lowering therapy use, and rheumatology encounters. Conversely, factors negatively associated included male sex, chronic kidney disease, urban residence, serum uric acid control, age, and certain racial categories.

Comment: I must admit that I had not considered gout as a pathway towards opiate addiction, as I don't prescribe opiates for gout. This study of a large Veterans Claims database found a significant increase in the risk of chronic opiate usage in patients with gout, indicating that we must be vigilant and careful to avoid starting opiates in these patients or ensuring that opiates are ceased once the flare is over. We need to educate our GPs and emergency department doctors not to start opiates in these patients.

Reference: 0240
Abstract

Variations in approach to the diagnosis and management of polymyalgia rheumatica among Australian rheumatologists

Authors: Yang V et al.

Summary: This study surveyed 79 Australian rheumatologists and trainees to assess opinions and practices related to diagnosing and managing polymyalgia rheumatica (PMR). Of the respondents, 76% completed the survey. Findings revealed diverse perspectives on PMR diagnosis criteria, with 23% considering bilateral shoulder involvement necessary and 37% insisting on elevated inflammatory markers. Imaging was viewed as useful in diagnostic uncertainty. Prednisolone at 15mg and a 12-month steroid wean had consensus for initial treatment. Steroid-sparing drugs, mainly methotrexate, were commonly prescribed, often in second or later relapses. Monitoring priorities included steroid side effects, pain, stiffness, fatigue, and physical function impact. Almost half recognised distinct patient populations with self-limiting disease and those requiring lifelong low-dose prednisolone.

Comment: Now that biological therapy for PMR appears to be around the corner, making an accurate diagnosis has become increasingly important. This poster from the South Australian group reflects the reality that many rheumatologists diagnose PMR without the classical presentation of bilateral shoulder involvement and elevated inflammatory markers. It reflects my experience that a significant number of patients require long-term steroids and that many patients are started on cDMARDs despite an absence of good data for their use. Rheumatologists will need to tighten up their diagnosis of PMR if they are going to use biologics for this condition, even though the studies have shown that these drugs appear to be safer in this age group than would have been predicted. Also, leakage of treatment will increase the costs to the community of these very expensive medications.

Reference: 0267
Abstract

The potential of an oral TNFα inhibitor with TNFR1 specificity

Authors: Fishbein A et al.

Summary: This double-blind, randomised, placebo-controlled clinical trial assessed the efficacy and safety of SAR441566, an oral TNFα inhibitor, in patients with mild-moderate psoriasis. The study included 26 participants receiving the TNFα inhibitor and 12 on placebo. Both groups were similar in baseline characteristics. No serious adverse events were reported, and all observed treatment-emergent adverse events were mild to moderate, with full recovery. By week 4, the TNFα inhibitor group demonstrated significant improvement in psoriasis severity, as indicated by adjusted mean % improvement in PASI (least squares mean ± standard error, 35.09 ± 4.47 versus 15.71 ± 6.33, p=0.009), TLS (% change 38.18 ± 4.33 versus 20.44 ± 6.18, p= 0.012), and IGA (58.3 versus 0%).

Comment: This is an interesting Phase 1 study of an oral TNFi demonstrating effectiveness in psoriasis. The compound binds TNFR1, reducing the inflammatory effects of TNF. It does not bind to TNFR2, through which TNF mediates its regulatory effects. I am looking forward to the studies in inflammatory arthritis. This drug may prove to be safer than the current non-specific TNFi.

Reference: 0443
Abstract

Microbiome transplantation prevents osteoarthritis in mice and is associated with immunophenotype changes

Authors: Dyson G et al.

Summary: In this study, adult male mice were orally inoculated with cecal contents from different mouse strains to investigate the impact of gut microbiota on OA. Mice with MRL cecal contents were protected from OA, evidenced by lower OARSI scores, synovitis, and osteophytes. Transplantation of MRL cecal contents into B6 mice and subsequent breeding also conferred protection to the F1 and F2 generations. However, the reverse transplantation worsened OA in B6 mice. The timing of transplantation relative to the destabilisation of the medial meniscus surgery influenced its effectiveness. Cecal microbiome composition correlated with OA outcomes, and immunophenotyping revealed changes in immune cell populations. These findings suggest a crucial role of gut microbiota in OA development and highlight potential therapeutic implications.

Comment: There has been a recent interest in the role of the microbiome in the development of osteoarthritis. This tantalising study demonstrates that protection from OA development in a mouse model of OA can be transferred by transplanting the microbiome from a mouse resistant to OA development. Also, the reverse was possible with an increase in OA in the resistant model when given the microbiome of the susceptible model. The researchers were also able to relate the changes in the microbiome to changes in circulating immune cells. Instead of a cartilage transplant in the future, we may be treating OA with faecal transplants.

Reference: 1581
Abstract

Non-TNFi b/tsDMARDs vs. TNFi in Rheumatoid Arthritis-Interstitial Lung Disease

Authors: England B et al.

Summary: This active-comparator, new-user study in the Veterans Health Administration from 2006 to 2018 focused on patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) initiating treatment with TNFi or non-TNFi biologics/JAK inhibitors. Among 1,046 eligible RA-ILD patients, 237 TNFi initiators were matched with 237 non-TNFi/JAKi initiators. The cohorts showed no significant differences in the primary outcome, respiratory hospitalisation, all-cause mortality, or respiratory-related death. Adalimumab and etanercept were the most frequent TNFi, while rituximab and abatacept were the most frequent non-TNFi/JAKi. Sensitivity analyses with modified cohort eligibility criteria also revealed no significant differences in outcomes between the two groups.

Comment: There were several presentations at the meeting of studies using target trial emulation with large clinical datasets with propensity score matching. I have seen the occasional patient in whom I have been concerned that TNFi has caused ILD, and there has been some recent concern for using TNFi in patients with ILD. This study of RA patients starting a TNFi was interesting because the matched non-TNFi group were patients mainly on rituximab, which we might consider a treatment for RA ILD. Yet it found no difference in the risk of death or respiratory hospitalisation. Multiple sensitivity analyses and subanalyses did not show any significant differences. At present, I would not stop a TNFi in a patient doing otherwise well and who develops RA ILD unless I plan to treat with rituximab.

Reference: 1582
Abstract

Comparison of two dosing schedules for oral methotrexate (split-dose versus single-dose) once weekly in patients with active rheumatoid arthritis

Authors: Prasad CB et al.

Summary: In this multicentre, open-label, randomised controlled trial involving patients with rheumatoid arthritis (RA) aged 18-60 and meeting specific criteria, 253 participants were randomised into split-dose (n=128) and single-dose (n=125) groups. The split-dose group showed a significantly lower disease activity score (DAS28) after 16 weeks of methotrexate (MTX) monotherapy than the single-dose group. The split-dose group also exhibited higher rates of positive responses in EULAR, ACR20, ACR50, and ACR70 criteria. Fewer patients in the split-dose group required additional DMARDs, and at 24 weeks, the split-dose group maintained a lower DAS28. However, there was no significant difference in health assessment questionnaire scores. Adverse events were generally minor, but the split-dose group had a higher frequency of transaminitis.

Comment: I have had some concerns in the past that dividing the methotrexate dose may increase adverse events for no real efficacy gain. This study of methotrexate 25 mg weekly in divided doses or single dose did not show any meaningful differences in clinical outcomes, with the primary outcome of EULAR moderate response not met but was associated with an increase in adverse events, particularly transaminase increases greater than twice the upper limit of normal (15.6% in the divided doses compared with 9.4% in the single dose group) which might lead to drug cessation or reduced dosing. There was also a numerical increase in gastrointestinal intolerance. Even though these differences in adverse event rates were not statistically significant, they are numerically of concern. I will not be changing how I use methotrexate.

Reference: 1583
Abstract

Romosozumab versus denosumab in high-risk patients treated with Glucocorticoids

Authors: Mok CC et al.

Summary: In this study, adult patients receiving prednisolone for at least 12 months with a moderate/high risk of osteoporotic fracture were randomised to receive romosozumab or denosumab over 12 months, followed by DEN for two more 6-month doses in both groups. The primary endpoint was the lumbar spine's change in bone mineral density (BMD). Romosozumab-treated patients showed a significant increase in spine BMD compared to denosumab-treated patients at month 12. Both groups demonstrated an increase in hip BMD, with no significant difference between them. Romosozumab patients experienced self-limiting injection site pain/redness more frequently. Adverse events were generally mild, and no serious adverse events were reported. The study suggests that romosozumab may be more effective than denosumab in increasing spine BMD in patients on long-term prednisolone.

Comment: Glucocorticoid-induced osteoporosis remains a major problem. In this three-year study of a typical at-risk patient group, one year of romosozumab significantly increased the spinal bone density at 12 months compared to denosumab. Both groups then went on to 2 years of denosumab, with the difference between treatments continuing out to 3 years. Therefore, pretreatment with romosozumab did not affect the response to denosumab. There was an equivalent small increase in hip BMD in both groups. About half the patients were on an oral bisphosphonate at the study entry, and the presenter could not comment on whether prior oral bisphosphonate treatment affected response. Interestingly, the romosozumab group had more fractures or worsening vertebral fracture deformities. Romosozumab, followed by denosumab, appears to be very effective at increasing BMD in the high-risk steroid group, although I will be keenly awaiting the longer-term fracture outcomes.

Reference: 2429
Abstract

A phase 3 study of repeat injection of TLC599 in osteoarthritis of the knee

Authors: Spencer-Green G et al.

Summary: This phase 3 study evaluated TLC599, a potential treatment for knee OA, in a randomised, double-blinded trial involving 506 patients with K-L Grade 2-3 OA. Patients received TLC599, DSP, or saline placebo injections. TLC599 demonstrated numerical and statistical superiority over placebo in WOMAC pain scores at all time points through week 24, with statistical significance at the primary endpoint, Week 12. For average daily pain, TLC599 was numerically and statistically superior to placebo during the first injection period, and at Week 12, it outperformed dexamethasone sodium phosphate. Patients receiving repeat TLC599 doses maintained pain reduction superiority through Week 52. The study concluded that TLC599 was well-tolerated, with no signs of adrenal insufficiency despite a transient reduction in cortisol levels.

Comment: I liked this poster because it was a plenary presented by an Australian rheumatologist. Secondly, it would be nice to have something effective to inject into an OA knee. This is a study of a liposomal preparation of dexamethasone sodium phosphate that demonstrated superior pain and functional improvements compared to a placebo injection. The benefit lasted six months, and this preparation was effective when repeated at about six months. This preparation was also generally more effective than the usual dexamethasone preparation we inject and was well tolerated. Nevertheless, the dexamethasone arm was also better than the placebo out to about six months but not as effective as the liposomal preparation. This could become the steroid preparation for an injection if and when it becomes available. The question remains whether this preparation will accelerate cartilage loss, which seems likely.

Reference: L19
Abstract

