Rheumatology Research Review™

Making Education Easy

Issue 23 - 2012

In this issue:

Abbreviations used in this issue

bDMARDS = biological disease modifying anti-rheumatic drugs; **DAS** = disease activity score; **lcSSc** = limited cutaneous systemic sclerosis; **MRI** = magnetic resonance imaging; **OA** = osteoarthritis; **PAP** = pulmonary artery pressure; **RA** = rheumatoid arthritis; **SLE** = systemic lupus erythematosus; **TNF** = tumour necrosis factor; **vWF** = von Willebrand factor

Welcome to the twenty-third issue of Rheumatology Research Review.

In this issue we review a large genome-wide association study that identified eight new loci conferring susceptibility to OA. We also review a meta-analysis in OA which found no clinically relevant benefit of viscosupplementation, but an increased risk for serious adverse events. In RA, we review a study that concluded methotrexate step-up therapy is a reasonable therapeutic strategy over more immediate intensive therapy, while another study reported that remission rates are higher if methotrexate induction therapy is initiated when disease activity is low. Two studies on systemic sclerosis raise more questions than answers and show a need for improved research in this area.

We hope you enjoy our selection for this edition and your comments and feedback are welcome.

If you have colleagues or friends within Australia who would like to receive our publication, send us their contact email and we will include them for the next issue.

Kind Regards,

Professor Graeme Jones

graeme.jones@researchreview.com.au

Identification of new susceptibility loci for osteoarthritis (arcOGEN): a genome-wide association study

Authors: arcOGEN Consortium and arcOGEN Collaborators

Summary: A large genome-wide association study (GWAS) was undertaken in 7410 patients with severe OA in the arcoGEN study and compared with 11,009 controls from the UK. All patients and controls were of European descent and 80% of patients had undergone total joint replacement. The most promising signals were replicated in an independent group of 7473 patients with OA and 42,938 controls from Iceland, Estonia, the Netherlands and the UK. Five genome-wide loci significant for association with OA were identified and a further three loci were just below the threshold for genome-wide significance (binomial test $p \leq 5.0 \times 10^{-8}$). The strongest association was found in variant rs6976 on chromosome 3 in the region of the *GNL3* gene, in perfect linkage disequilibrium with variant rs11177. Levels of nucleostemin, the encoded protein of *GNL3*, were raised in chrondrocytes from patients with OA in functional studies. The other significant loci were on chromosome 9 close to *ASTN2*, chromosome 6 between *FILIP1* and *SENP6,* chromosome 12 close to *KLHDC5* and *PTHLH*, and in another region of chromosome 12 close to *CHST11*. One of the sub-threshold loci was within the *FTO* gene, which is involved in the regulation of bodyweight and therefore a strong risk factor for OA.

Comment: The identification of genes for osteoarthritis has proven very challenging. This latest and largest attempt doesn't shed much extra light. Why is this? We know that genes make a major contribution but both linkage and GWAS approaches have struggled. I suspect this is because of the problem with defining phenotype, e.g. hip OA is not the same as knee OA and those having joint replacement are different in other ways, notably pain. Each of the components of OA (e.g. obesity, muscle strength, bone marrow lesions, cartilage defects and meniscal tears) have their own genetic component so there may be more bang for the buck studying these features separately.

Reference: Lancet 2012;380(9844):815-823
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60681-3/abstract

Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis

Authors: Rutjes AWS et al

Summary: This meta-analysis of 89 randomised trials involving 12,667 adults with knee OA found that viscosupplementation was associated with a small and clinically irrelevant benefit and an increased risk for serious adverse events. The meta-analysis included randomised trials in any language from 1966 to January 2012. Intra-articular injection of hyaluronic acid was compared with sham control in 68 trials and non-intervention in 21 trials. Follow up was greater than 3 months in 40 trials, but trial quality was generally low and safety data were often not reported. Viscosupplementation was shown to moderately reduce pain in 71 trials involving 9617 patients with an effect size of -0.37 (95% CI -0.46 to -0.28). There was important heterogeneity between trials with effect size associated with trial size, blinded outcome assessment and publication status. A clinically irrelevant effect size was shown in 18 large trials (5094 patients) with blinded outcome assessment. Viscosupplementation was shown to increase the risk for serious adverse events in 14 trials involving 3667 patients (relative risk 1.41; 95% CI 1.02 to 1.97).

Comment: The roosters will be happy about this. As is common, methodological rigour makes a large difference to trial outcomes. In this case, blinding the assessors led to no effect indicating the need for blinding and an equivalent placebo. This is one reason why I am a critic of pragmatic trials (no real blinded comparator) because adequate blinding becomes impossible and patient expectation becomes everything.

Reference: Ann Intern Med 2012;157(3):180-191
http://annals.org/article.aspx?articleid=1305531

Low-level lead exposure and the prevalence of gout: an observational study

Authors: Krishnan E et al

Summary: Blood lead levels considered acceptable by US national standards (<1.21 µmol/L or <25 µg/dL) were associated with increased prevalence of gout and hyperuricemia in a population-based cross-sectional study. The NHANES study involved 6153 adults aged ≥40 years with an estimated glomerular filtration rate >10 mL/min per 1.73 m^2. The prevalence of gout was 6.05% (95% CI 4.49% to 7.62%) for patients in the highest quartile of blood lead levels (mean 0.19 µmol/L or 3.95 µg/dL) compared with 1.76% (95% CI 1.10% to 2.42%) for patients in the lowest quartile (mean 0.04 µmol/L or 0.89 µg/dL). Each doubling of blood lead level was associated with an unadjusted odds ratio of 1.74 (95% CI 1.47 to 2.05) for gout and 1.25 (95% CI 1.12 to 1.40) for hyperuricemia. The risk for gout was 3.6-fold higher in the highest blood lead level quartile than the lowest quartile after adjustment for renal function, diabetes, diuretic use, hypertension, race, body mass index, income and education level. Similarly, the risk for hyperuricemia was 1.9-fold higher after these adjustments.

Comment: This is a cross-sectional study so may be biased but is intriguing nevertheless. We all know lead poisoning increases the risk of gout but this study suggests a dose response even in very low levels. This may be reverse causation in that the poorest levels of US society have more gout and will likely have greater lead exposure. Notwithstanding, we can get rid of lead so worth thinking about.

Reference: Ann Intern Med 2012;157(4):233-241
http://annals.org/article.aspx?articleid=1351359

Rheumatology Research Review™

Independent commentary by Professor Graeme Jones.

Graeme is Professor of Rheumatology and Epidemiology and Head of the Musculoskeletal Unit at the Menzies Research Institute as well as Head of the Department of Rheumatology at Royal Hobart Hospital. He is also the Medical Director of the Arthritis Foundation of Australia.

Disclosure: Professor Jones contributes to advisory boards for many different pharmaceutical companies.

A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the Treatment of Early Aggressive Rheumatoid Arthritis trial

Authors: Moreland LW et al

Summary: The Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) study assessed whether it is better to intensively treat all patients with early RA with methotrexate combination therapy or to reserve this approach for patients who do not respond to methotrexate monotherapy. In the 2-year double-blind, placebo-controlled study, patients were randomised to receive either immediate treatment with methotrexate combination therapy (methotrexate + etanercept or methotrexate + sulfasalazine + hydroxychloroquine) or step-up from methotrexate monotherapy to either of the combination therapies. Patients receiving monotherapy were stepped-up to combination therapy at week 24 if their DAS in 28 joints using erythrocyte sedimentation rate (DAS28-ESR) was ≥3.2. At the beginning of the step-up period at week 24, DAS28-ESR was significantly reduced in patients who received immediate combination therapy compared with those in the step-up groups (3.6 vs 4.2; p<0.0001). There were no differences between the combination-therapy regimens at week 24. During weeks 48-102, there were no differences in mean DAS28-ESR between patients randomised to immediate combination therapy and step-up therapy. At week 102, treatment with methotrexate + etanercept had a significant radiographic benefit compared with methotrexate + sulfasalazine + hydroxychloroquine (0.64 vs 1.69; p=0.047). The authors concluded that 'initial use of methotrexate monotherapy with the addition of sulfasalazine plus hydroxychloroquine (or etanercept, if necessary, after 6 months) is a reasonable therapeutic strategy for patients with early RA.'

Comment: This abstract has a lot of information and head-to-head trials are a little rare. If I read it correctly, triple therapy is clinically similar to methotrexate and etanercept in combination. But X-ray outcomes are modestly worse in the triple therapy arm, supporting the use of traditional step-up or combination therapy and then using bDMARDs in non responders.

Reference: Arthritis Rheum 2012;64(9):2824-2835
http://onlinelibrary.wiley.com/doi/10.1002/art.34498/abstract

Inflammation associated anemia and ferritin as disease markers in SLE

Authors: Vanarsa K et al

Summary: This study determined the relationship between ferritin and transferrin and disease activity in patients with SLE. Protein array showed significantly elevated levels of ferritin in the urine and serum of SLE patients compared with healthy controls. Increased ferritin levels correlated with disease activity and anaemia as well as inflammatory cytokine titers. Urine transferrin levels were elevated in active SLE patients and serum transferrin levels were reduced.

Comment: I have struggled with how to monitor SLE. Iron measures seem attractive. In this case, serum ferritin and urine transferrin. The authors state they correlate with other measures but this is modest so the key question is whether they are better predictors of hard outcomes over time like death, thrombosis, flares, etc.

Reference: Arthritis Res Ther 2012;14(4):R182
http://arthritis-research.com/content/14/4/R182

Treatment of systemic sclerosis complications: what to use when first-line treatment fails—a consensus of systemic sclerosis experts

Authors: Walker KM et al

Summary: In an effort to standardise management of systemic sclerosis, 117 experts were sent three surveys to gain consensus on treatment of systemic sclerosis complications. While there was generally good agreement for first-line treatments, there were discrepancies in drug choices for second-line therapy. First-line therapies were agreed as: angiotensin-converting enzyme inhibitors for scleroderma renal crisis; endothelin receptor agonists for mild pulmonary arterial hypertension; calcium channel blockers for Raynaud's phenomenon and prevention of digital ulcers; intravenous cyclophosphamide and mycophenolate mofetil or azathioprine for induction treatment in interstitial lung disease/pulmonary fibrosis and mycophenolate mofetil for maintenance; methotrexate for inflammatory arthritis; and mycophenolate mofetil for skin involvement after methotrexate. For gastroesophageal reflux disease, 72% would exceed the maximum recommended proton pump inhibitor dose if required.

Comment: Put ten rheumatologists in a room and you may get ten different answers especially if it is scleroderma. This attempt at consensus among 117 experts is one of the least consensual I have seen, probably indicating the paucity of good quality trials to drive these decisions. Nevertheless, this is state of the art in 2012 and has advanced a little since Bywaters made his pronouncement from the mountain in 1969.

Reference: Semin Arthritis Rheum 2012;42(1):42-55
http://www.semarthritisrheumatism.com/article/S0049-0172(12)00017-0/abstract

Remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis (the IMPROVED study)

Authors: Wevers-de Boer K et al

Summary: The efficacy of methotrexate 25 mg/week and a tapered high dose of prednisone was determined in 610 patients with recent onset RA or undifferentiated arthritis. The initial prednisone dose of 60 mg/day was tapered to 7.5 mg/day over 7 weeks. Remission rates after 4 months were similar regardless of the criteria used to classify the disease; 61% in patients with RA classified using the 2010 ACR/EULAR criteria, 58% in patients classified using the 1987 ACR criteria, and 65% in patients with undifferentiated arthritis. Patients who were positive for anticitrullinated protein antibodies (ACPA) had a higher rate of remission than patients who were negative for these proteins (66% vs 55%; p=0.001). They also had a lower mean baseline DAS (3.2 vs 3.6; p<0.001). Independent predictors for remission were male sex, low joint counts, DAS and Health Assessment Questionnaire, low body mass index and ACPA positivity. The authors concluded that 'initiating treatment while disease activity is relatively low results in more remission.'

Comment: My drinking mates in rheumatology will know that I think we under-dose methotrexate when commencing it. This study looked at methotrexate 25 mg weekly to start with tapering prednisone and found a 60% remission rate after 4 months. To be fair, this is uncontrolled, in early disease and we don't know how it goes as monotherapy, but this will provide grist for my mill.

Reference: Ann Rheum Dis 2012;71:1472-1477
http://ard.bmj.com/content/71/9/1472.abstract

Baseline vWF factor predicts the development of elevated pulmonary artery pressure in systemic sclerosis

Authors: Barnes T et al

Summary: This study examined the ultility of vWF as a biomarker to predict disease manifestations in patients with lcSSc. Logistic regression models showed that baseline serum vWF concentrations were able to predict the future development of elevated pulmonary artery pressure (PAP) >40 mmHg (p=0.001). The authors commented that 'screening patients with lcSSc for vWF may identify a group at risk of developing pulmonary artery hypertension' and suggested that 'these patients could potentially be targeted with agents that stabilize the endothelium, e.g. statins.'

Comment: This looked interesting so I went and read the paper. It raised more questions than answers. vWF is a predictor of development of PAP >40 mmHg (especially >150 mmHg) and maybe this is independent of baseline PAP (the table does not make this totally clear). However, it correlates with a number of other measures like D_{LCO} and these aren't adjusted for, nor are we given their predictive ability to compare. What we want is something that is better than or adds to existing measures, so the jury is scratching their heads about this paper.

Reference: Rheumatology 2012;51(9):1606-1609
http://rheumatology.oxfordjournals.org/content/51/9/1606.abstract

Dyslipidemia and changes in lipid profiles associated with rheumatoid arthritis and initiation of anti–tumor necrosis factor therapy

Authors: Curtis JR et al

Summary: This retrospective database study investigated the frequency of lipid testing in OA and RA patients in clinical practice. Patients with RA were less likely to be tested for hyperlipidemia and had more favourable lipid profiles than patients with OA. Over a median ≥2-year follow-up, 62% of RA patients and 69.8% of OA patients had ≥1 lipid test. Both mean total cholesterol and LDL cholesterol for RA patients were 4 mg/dl lower than for OA patients (p<0.0001). There was no difference in HDL cholesterol. Suboptimal LDL cholesterol levels ≥130 mg/dl were evident in 25.2% of RA patients. TNF inhibitor therapy initiated in 96 patients with RA, who were not receiving lipid-lowering therapy, increased total cholesterol by 5.4 mg/dl and LDL cholesterol by 4.0 mg/dl. The impact on cardiovascular outcomes in RA patients was not assessed and requires further study.

Comment: Some interesting snippets in this database study. OA is more frequently tested for lipids than RA and RA subjects have lower levels. Does this reflect greater comorbid illness like hypertension and diabetes in the OA population? Probably. Does it reflect a concentration on disease control as the best way to change cardiovascular risk in RA? Maybe. Lipid levels increased with TNF agents and they do with IL-6 blockade so maybe lipids aren't the key. I tend to leave lipids to the GP anyway, but a lot of patients weren't adequately controlled. Does this reflect taking medications for asymptomatic conditions or statin muscle disease. Again I suspect both have a role to play even if statins may protect against OA!

Reference: Arthritis Care Res 2012;64(9):1282-1291
http://onlinelibrary.wiley.com/doi/10.1002/acr.21693/abstract

Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study)

Authors: Guermazi A et al

Summary: This observational study used MRI to determine the prevalence of structural lesions in the knee associated with OA in 710 adults with no radiographic evidence of OA. Prevalence of 'any abnormality' detectable by MRI was 89%. The most common abnormality was osteophytes (74%), followed by cartilage damage (69%) and bone marrow lesions (52%). In this population of adults aged >50 (mean 62.3 years), the prevalence of all types of abnormalities detectable by MRI increased with age. BMI (mean 27.9) had no effect on the prevalence of any abnormalities. The prevalence of at least one type of abnormality was high in both painful (90-97%, depending on pain definition) and painless (86-88%) knees.

Comment: Trust the Americans to reinvent the wheel. There has been ten years of work internationally including many from Flavia Cicuttini and myself trying to identify (very successfully) the structural changes that occur in the knee prior to radiographic OA becoming evident. There are many and the sequence of events is becoming clear enough that we can embark on trials. Few of us have normal knee MRI scans after age 40. Surprise, surprise, the Bostonians have found the same. They managed to do this without referring to or maybe even reading a great number of papers on the area (with the exception of their own) and what is more got it past the BMJ which is notoriously difficult to put one over. They deserve me buying them a drink for this and pouring it over their heads!

Reference: BMJ 2012;345:e5339
http://www.bmj.com/content/345/bmj.e5339?view=long&pmid=22932918

