

American College of Rheumatology Conference Review™



Making Education Easy

Chicago, Illinois, USA, 4–9th November 2011

In this issue:

- Advances in SLE
- Treatment strategies in early RA
- Biological DMARD withdrawal
- Response to pneumococcal vaccine
- Osteoarthritis therapy
- CAD risk in RA
- Periodontal disease and RA
- To methotrexate or not with tocilizumab
- Do we really need other DMARDS in SpA?
- Tofacitinib and structural damage in RA

Welcome to this review of the American College of Rheumatology (ACR) 2011 Annual Scientific Meeting, a locally focused summary of some of the latest and most exciting developments in rheumatology.

This Review has been created to allow those unable to attend, but with a keen professional interest in research in rheumatic diseases, such as rheumatoid arthritis (RA), osteoarthritis (OA) and spondyloarthropathies (SpAs), to access a summary of significant abstracts presented that are likely to affect current practice. Selection and review of the research has been carried out independently by Professor Graeme Jones, who attended the ACR 2011 Annual Scientific Meeting during November 4–9, 2011, in Chicago, Illinois, USA.

Abstracts from the meeting have been published in *Arthritis Rheum* 2011;63(10 Suppl) and can be downloaded from http://www.rheumatology.org/education/annual/2011_abstract.pdf (18.7MB).

I hope you find this conference review stimulating, and I look forward to your feedback.

Kind Regards,

Dr Janette Tenne

Medical Research Advisor

janette.tenne@researchreview.com.au

Advances in SLE

This session had a number of interesting abstracts. In two abstracts analysing the same data, abatacept had totally different results for renal lupus as additional therapy to those on prednisone and mycophenolate mofetil. It did not meet its primary outcome (abstract 2469). However, it may have been that this bar was set too high. When the data were reanalysed using criteria previously used in other renal lupus trials, there were significant improvements for virtually all endpoints (abstract 2474) suggesting the choice of outcome measure is key for trial results. Discussion afterwards was why not use a continuous outcome rather than categorical? I concur. Also in the session were data showing fish oil did not work for disease activity or CV measures in SLE. Indeed, it increased LDL cholesterol levels (abstract 2471). In a post-hoc analysis, belimumab also appeared to work for renal disease (abstract 2472). The most interesting paper in my view was the use of a novel technology to create anti-interferon (IFN)- α antibodies (see below). This only worked in the two-thirds of subjects with a detectable IFN- α signal, and this signal was in turn related to complement and dsDNA levels, and creating the antibody decreased these markers, which is encouraging.

Abstract 2470: Active immunization against IFN α with IFN-Kinoid in SLE patients is safe, immunogenic and induces down-regulation of IFN-mediated genes

Authors: Houssiau FA et al

Summary: Patients with mild-to-moderate seropositive lupus (n=28; SLEDAI 4–10) received IM IFN- α -Kinoid (Neovacs SA, Paris, France; a recombinant human IFN- α conjugated to KLH as a carrier protein, inactivated and adjuvanted with ISA-51 emulsion) 30mg, 60mg, 120mg or 240mg or placebo on days 0, 7, 24 and, optionally, 84, in this phase I–II study. All immunised participants experienced a dose-related anti-IFN- α antibody response, with antibodies peaking after the last dose and declining thereafter. Baseline PBMC transcriptomic studies indicated that the participants clustered into two groups according to the presence versus absence of an IFN- α signature; significantly higher dsDNA antibody titres and significantly lower C3 and C4 levels were seen in those with a positive signature. In the participants with a baseline IFN signature, follow-up transcriptomic studies performed as early as 38 days after the first injection of IFN- α -Kinoid in participants with a baseline IFN signature revealed that compared with placebo, IFN- α -Kinoid was associated with significant downregulation of IFN-induced gene expression, and, more generally, of SLE over-expressed genes as a whole. The safety profile was very favourable, with only a few minor, transient local and systemic reactions associated with immunisation.

**Psychiatry
Research Review**

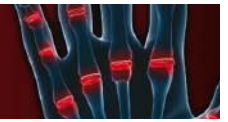
[Click here to subscribe](#)

**Pain
Management
Research Review**

[Click here to subscribe](#)

**Parkinson's
Disease
Research Review**

[Click here to subscribe](#)



Treatment strategies in early RA

This session had a bit to ponder. In a nonindustry sponsored trial in bad-prognosis RA of short duration (3.6 months), four options were compared. Methotrexate/etanercept and triple therapy were both superior to methotrexate monotherapy at 24 weeks. However, those with a DAS >3.2 were stepped up to etanercept after 24 weeks. By 12 months, there were no differences between any of the groups in either disease activity or x-ray progression, validating the 6-month rule in Australia and forcing me to change my view that biological DMARDs should be started from day 1 in bad-outlook subjects.

Abstract 1696: Validation of methotrexate first strategy in early rheumatoid arthritis

Authors: O'Dell JR et al

Summary: In this study, 755 patients with early poor-prognosis RA were randomly assigned to receive initial therapy with methotrexate monotherapy (n=379) or combined with either etanercept or sulfasalazine plus hydroxychloroquine. At 24 weeks, 28% of monotherapy recipients had achieved low disease activity, and the remainder were stepped up to combination therapy. A durable response was seen at week 102 among participants who continued on monotherapy (mean DAS28 score 2.7 versus 3.0 for those who received immediate combination therapy [p=0.15]). Methotrexate monotherapy recipients also experienced less x-ray progression than immediate combination therapy recipients (TSS 0.1 vs. 1.1; p=0.10). DAS28 scores and x-ray progression were similar in the immediate combination therapy at start of therapy and in the step-up group 12 weeks after starting combination therapy, and also at 102 weeks. No differences were seen between the two types of immediate combination therapy.

Biological DMARD withdrawal

There were two trials covering induction therapy with adalimumab in early disease (abstracts 1698 and 1699). Both showed that adalimumab could be withdrawn after 6 months without marked worsening in most patients. They found slightly different results for x-ray progression, with one study progressing and the industry-funded study not. These suggest that adalimumab could cautiously be withdrawn in early disease if we can get the HIC to agree to restart if things get worse.

Abstract 1699: Withdrawal of adalimumab in early rheumatoid arthritis patients who attained stable low disease activity with adalimumab plus methotrexate

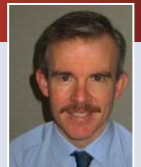
Authors: Kavanaugh A et al

Summary: This two-period phase 4 trial enrolled methotrexate-naïve adults with active RA of <1 year duration and either >1 erosion or anti-CCP-positive. For the first period, participants were randomised to receive methotrexate with either placebo or adalimumab for 26 weeks, and for the second period, the combination therapy participants who had achieved stable low disease activity status were rerandomised to continue combination treatment (n=105) or replacement of adalimumab with placebo (n=102) out to week 76. Most adalimumab-withdrawal participants maintained good clinical, radiological and functional responses during the second period, with stable composite outcomes predicted by lower baseline Health Assessment Questionnaire scores in this group (p=0.01). However, higher levels of disease control were seen in participants who continued adalimumab versus those in whom it was withdrawn, suggesting there are some who may benefit from continued combination therapy.

ACR 2011 Conference 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.



MY RA IS MORE ACTIVE THAN ME

Before prescribing please review the Approved Product Information by [CLICKING HERE](#). PBS prices: ACTEMRA concentrate for injection 80 mg in 4 mL: \$186.88, 200 mg in 10 mL: \$467.20, 400mg in 20 mL: \$934.40. Further information is available on request from: Roche Products Pty Limited, ABN 70 000 132 865, 4-10 Inman Road, Dee Why 2099. ©Registered Trademark 08/11 MN37542782 EMVACTO144A

ACTEMRA (tocilizumab) PBS Information: Authority Required. Refer to PBS Schedule for full information.





Response to pneumococcal vaccine

This was an interesting observational study looking at response to vaccination in different categories of RA. Rituximab or methotrexate monotherapy appeared to block response. Interestingly, anti-TNF monotherapy didn't interfere and anti-TNFs appeared to ameliorate the methotrexate effect in combination. Could this be because they normalise B-cell antigen expression? Tocilizumab also appeared to have little effect based on the poster.

Abstract 398: Rituximab and methotrexate but not TNF-blockers are associated with impaired antibody response following pneumococcal vaccination using 7-valent conjugate vaccine (Prevenar®) in patients with established rheumatoid arthritis

Authors: Kapetanovic MC et al

Summary: This study investigated the effects of antirheumatic treatments on antibody response in patients with established RA (n=294) or SpA (n=86) who had received a single IM dose of 7-valent conjugate pneumococcal vaccine (Prevenar®) 0.5mL. Compared with control patients receiving NSAIDs/analgesics, antibody response ratios (ARRs) were significantly lower in participants receiving all other RA therapies, except for anti-TNF monotherapy, for both IgG 23F- and 6B-specific serotypes. Impaired antibody response was predicted by treatment with both rituximab and methotrexate (adjusted odds ratios 0.5 [95% CI 0.31–0.97] and 0.09 [0.03–0.3], respectively), but not anti-TNF agents; insufficient statistical power prevented detailed analyses of the effect of abatacept and tocilizumab.

Osteoarthritis therapy

Diet plus exercise was again shown to be superior to either alone for OA symptoms (abstract 722). Tart cherry juice, equivalent to 45 cherries per day, may improve OA symptoms (abstract 1092), even though this study was done by a gout researcher (where there is a priori evidence that it may work). Low-dose fish oil was superior to high-dose fish oil over 2 years for knee OA symptoms (see below) in both intention-to-treat and per-protocol analyses. This was an Australian multicentre trial. Clearly this was opposite to our hypothesis. The oil used to dilute the low-dose fish oil and maintain binding was safflower oil, which was thought to be inert, but these results suggest the combination may be the best option. The slow and continuing improvement may also imply disease modification, but the MRI results are not in at this stage.

Abstract 1093: Fish oil in knee osteoarthritis: a two year randomized, double-blind clinical trial comparing high dose with low dose

Authors: Hill CL et al

Summary: Patients aged >40 years with regular knee pain due to OA (n=202) were randomly allocated to receive high-dose fish oil liquid (18% EPA and 12% DHA) or low-dose fish oil (1:9 ratio of fish and 'Sunola' oils) 15 mL/day. Clinically important improvements from baseline in WOMAC pain (primary endpoint) and disability scores were seen in both groups during the 24-month trial, and while there were no between-group differences during the first 12 months, improvements in the low-dose group were greater at 24 months compared with the high-dose group (-5.2 vs. -2.8 and -12.7 vs. -8.0 for pain and disability, respectively). In addition, low-dose recipients showed a trend for a better OARS response at 24 months. Furthermore, dropout was more common and occurred earlier in the high-dose arm than the low-dose arm (34.6% vs. 19.8% and 3 vs. 7.5 months [median], respectively).

CAD risk in RA

This well-conducted observational study indicated both methotrexate and anti-TNF therapy decreased the risk of CAD by about a third. What was novel is that there seemed to be a duration effect. With methotrexate, the reduction was observed after 22 months, and 17 months for anti-TNF agents. This may have been biased by only good responders staying on treatment this long, but also suggests that control of inflammation is key for reducing cardiovascular risk in RA.

Abstract 719: Reduced cardiovascular risk with use of methotrexate and tumor necrosis factor-α inhibitors in patients with rheumatoid arthritis

Authors: Bozait-Gluosniene R et al

Summary: The respective effects of methotrexate and TNF-α inhibitors on coronary artery disease (CAD) were investigated in a cohort of 1829 patients with RA and without pre-existing CAD. Cox proportional hazard regression models revealed that compared with nonusers, the risk of incident CAD was significantly lower with: i) any duration of methotrexate use (adjusted hazard ratio 0.54 [95% CI 0.37–0.77; p=0.001]); ii) methotrexate use for >24 months (0.33 [0.22–0.50; p<0.001]); iii) any duration of TNF-α inhibitor use (0.54 [0.30–0.95; p=0.03]); and iv) TNF-α inhibitor use for >24 months (0.24 [0.12–0.51; p<0.001]).

Periodontal disease and RA

There were many abstracts on this issue. Periodontal disease is more common in RA. A specific organism, *Porphyromonas gingivalis*, is the only known prokaryote to possess a bacterial peptidylarginine deiminase, which in combination with *P. gingivalis*-specific proteases, the arginine gingipains, citrullinates peptides from both α-enolase and fibrinogen. In this abstract, there was a positive correlation between periodontal disease and disease activity levels and also between ACPA titres and IgM anti-*P. gingivalis* levels. This is still association, but is becoming more convincing. Will treating this bug make a difference, and will this depend on stage of disease?

Abstract 2175: Prevalence of periodontitis is high in rheumatoid arthritis patients and correlated to disease activity

Authors: de Smit MJ et al

Summary: Relationships between periodontitis and RA were explored in 95 dentate patients with RA. Dutch periodontal screening index (DPSI) category C (require extensive periodontal examination) was present in 27% of the cohort, compared with 12.5% reported in normal adults from the same region. Furthermore, these RA patients had significantly higher DAS scores, C-reactive protein levels and IgMRF levels than those from DPSI categories A and B. *P. gingivalis* was detected in 17% of the cohort, 56% of whom were DPSI category C. *P. gingivalis*-positive patients also had significantly increased IgG anti-*P. gingivalis* titres (p=0.002). Positive correlations were seen between: i) ACPA and IgM anti-*P. gingivalis* levels (p=0.017); ii) ACPA levels and IgMRF titres (p<0.0001); and iii) serum and gingivocrevicular ACPA titres (p<0.0001).

To methotrexate or not to methotrexate with tocilizumab

AMBITION suggested tocilizumab worked pretty well without methotrexate and had less abnormal liver function tests. ACT-RAY suggested disease activity did not worsen for virtually all endpoints when methotrexate was withdrawn at tocilizumab initiation in methotrexate inadequate responders. The question was, does this affect x-ray damage? The answer is that rates are the same in both groups. I have tended to wait for 3 months to stop methotrexate when starting tocilizumab because of my fear of not meeting the HIC criteria, but this study suggests we can stop earlier if we want to.

Abstract 2628: Double-blind study of tocilizumab plus methotrexate vs tocilizumab plus placebo in patients with active rheumatoid arthritis despite prior methotrexate: progression of structural damage, quality of life, and physical function at 24 weeks

Authors: Dougados M et al

Summary: Participants from the ACT-RAY study being treated with stable doses of methotrexate for RA were randomised to add-on tocilizumab 8 mg/kg every 4 weeks (n=279) or switched to tocilizumab (plus placebo; n=277). At 24 weeks, there were no significant differences between the tocilizumab plus placebo and tocilizumab plus methotrexate arms for change in DAS28 remission rates (primary endpoint; 34.8% and 40.4%, respectively; p=0.19) or other efficacy endpoints. Near complete arrest of structural damage progression led to improved quality of life in both groups, but the between-group differences were not significant. Safety data were consistent with previous findings associated with tocilizumab.



Do we really need other DMARDS in SpA?

This large study identified a number of risk factors for disease response to anti-TNF agents in three SpA conditions. However, for all three conditions, there were no benefits from cotherapy with DMARDs, suggesting current guidelines are appropriate.

Abstract 2637: The effect of DMARD co-therapy on anti-TNF drug retention in 1630 spondyloarthritis patients

Authors: Nissen MJ et al

Summary: These researchers investigated the impact of concomitant DMARD therapy on anti-TNF drug retention in patients (mean age 44 years; from the Swiss Clinical Quality Management registries) with suspected axial SpA (n=1060), psoriatic arthritis (n=535) or undifferentiated SpA (n=35) followed for a median of 3.2 years. A total of 2158 anti-TNF courses were recorded, with 68.9% and 31.1% monotherapy and cotherapy, respectively, and adalimumab, etanercept and infliximab prescribed in 37.3%, 33.7% and 29.1% of patients, respectively. DMARDs included methotrexate, sulfasalazine and leflunomide in 72.0%, 20.9% and 14.0%, respectively. The findings support the current recommendation that DMARD cotherapy provides no additional benefit over anti-TNF monotherapy in SpA (adjusted hazard ratio 1.06 [95% CI 0.90–1.24]). Male patients and those with longer disease duration had longer anti-TNF drug retention (odds ratios 0.79 [p=0.003] and 0.98 [p<0.001], respectively), while those with lower baseline disease activity and previous anti-TNF exposure exhibited shorter anti-TNF retention (1.20 and 1.60, respectively; p<0.001 for both). Anti-TNF survival did not differ among the various anti-TNF agents.

Tofacitinib and structural damage in RA

Tofacitinib (CP-690,550), an oral Janus kinase inhibitor, is effective for signs and symptoms of RA. However, its effect on signs and symptoms seems a bit more modest than methotrexate plus an anti-TNF. This study suggested that it virtually halted radiographic progression over 6 months, while the placebo arm had the usual rate of change we have seen in clinical trials in recent years (around 1 unit per year). This suggests a disconnect with greater effects on structure. As an oral agent, it will be interesting to see where it is positioned.

Abstract 2592: Tofacitinib (CP-690,550), an oral Janus kinase inhibitor, in combination with methotrexate reduced the progression of structural damage in patients with rheumatoid arthritis

Authors: van der Heijde D et al, and the ORAL Scan investigators

Summary: This phase 3 study randomised patients receiving stable doses of methotrexate (n=797) 4:4:1:1 to receive tofacitinib 5mg or 10mg twice daily or placebo advanced to either tofacitinib 5mg or 10mg at 3 months if no response or at 6 months. The higher tofacitinib dose was superior to placebo for efficacy (ACR20 response rate at 6 months, mean change in HAQ-DI at 3 months and proportion of participants achieving DAS28-4(ESR) <2.6 at 6 months) and for structure preservation (mean change in baseline modified Total Sharp Score [mTSS] at 6 months), while the lower dose was superior to placebo for ACR20 response rates, but not other efficacy endpoints or change in mTSS. Secondary analyses revealed that both tofacitinib doses were associated with significantly greater proportions of participants with no radiographic progression (mTSS change ≤0.5) or no new erosions than placebo. Subgroup analyses showed a consistent pattern of structure preservation among participants with predictors of poor prognosis. Adverse events associated with tofacitinib included mostly mild infections, decreased neutrophil counts, increased LDL and HDL cholesterol levels and small serum creatinine level increases.



tocilizumab

ACTEMRA®

A BIOLOGICAL CHOICE IN ACTIVE AGGRESSIVE RA¹⁻⁵

Roche

PBS Information: Authority Required. Refer to PBS Schedule for full information.

Before prescribing please review the Approved Product Information by [CLICKING HERE](#). PBS prices: ACTEMRA concentrate for injection 80 mg in 4 mL: \$186.88, 200 mg in 10 mL: \$467.20, 400mg in 20 mL: \$934.40. References: 1. ACTEMRA Approved Product Information, January 2011. 2. Genovese MC *et al.* Poster presented at: American College of Rheumatology 72nd Annual Scientific Meeting; October 2008; San Francisco, CA, USA. Poster 987. 3. Smolen JS *et al.* *Lancet* 2008;371:987-997. 4. Burmester G *et al.* *Ann Rheum Dis* 2011;70:755-9. 5. Nishimoto N *et al.* *Ann Rheum Dis* 2009;68:1580-1584. Further information is available on request from: Roche Products Pty Limited, ABN 70 000 132 865, 4-10 Inman Road, Dee Why 2099. ©Registered Trademark 08/11 MN37542782 EMVACT0144B

Research Review is an independent medical publishing organisation producing electronic journals in several specialist areas. These journals provide summaries of the 'must see' studies from the most respected medical journals in the world together with a local specialist commentary indicating why they matter. Research Review publications are intended for Australian medical professionals.

Privacy Policy: Research Review will record your email details on a secure database and will not release it to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time. **Disclaimer:** This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

Research Review publications are intended for Australian health professionals.