American College of Rheumatology

Conference Review

Making Education Easy

ACR Annual Scientific Meeting, Philadelphia 2009, Pennsylvania, USA

In this issue:

Welcome

to the ACR Conference Review 2009, a locally focused summary of some of the latest and most exciting developments in rheumatology research presented at the ACR Annual Scientific Meeting.

This Review has been created to allow those unable to attend, but with a keen professional interest in rheumatology research, to access a summary of significant clinical studies presented that are likely to affect current practice. Selection and review of the research is carried out independently by Dr Andrew Harrison, who attended the ACR Annual Scientific Meeting, held in Philadelphia, USA.

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

Kind regards,

Dr Chris Tofield
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The Opening Lecture

The opening lecture commemorated the 75th anniversary of the ACR and described advances in rheumatology from the beginning of the nineteenth century to the formation in 1934 of the association that would become the ACR. Dr Dorwart described the important publications in the nineteenth century, including the intriguing fact that, during the American Civil War, rheumatism was the leading cause of illness in black soldiers and the third leading cause in white soldiers.

Ralph Schumacher outlined the advances of the twentieth century that included, without bias, the discovery of urate crystals in tophi in 1947, the ARA gout criteria in 1977 and Ian Prior's epidemiology of gout in Polynesians. He reminded us that not all discoveries have been successful, and cited rofecoxib and the prosorba column as examples of therapeutic failures. Included in his list of important advances were ACE inhibitors in scleroderma renal crisis and cyclophosphamide in vasculitis.

Dr Christian outlined the history of the ACR from the early committees comprised largely of hydrologists to the formation of the ARA in the mid 1930s, the first female president in the 1960s and the configuration of the modern ACR in 1988.

Independent commentary by Dr Andrew Harrison. Dr Harrison is a senior lecturer in the Department of Medicine at the University of Otago and Medical Advisor to Arthritis New Zealand. He is a practising specialist at the Wellington Regional Rheumatology Unit with a particular interest in research of inflammatory arthritis.

About Research Review

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Genome-wide association scans

Professor Peter Gregerson gave a State Of The Art lecture on the genetics of rheumatoid arthritis (RA). Genome wide association studies (GWASs) have identified a number of susceptibility loci for RA, and specific genes within these loci are gradually being discovered, although the mechanisms whereby these genes and their products mediate disease is not always well understood. The RA susceptibility genes account for only a small portion of the total heritability, and the remainder may be made up of numerous rare alleles that do not turn up in GWASs.

E Stahl (Boston) presented a meta-analysis of six RA GWASs in European seropositive RA patients. In addition to the previously described loci, statistical significance was found for several other SNPs, many of which were shared with other autoimmune diseases. *PADI4* was not strongly correlated with RA in this sample of over 5000 patients.

Genome-wide association study of systemic sclerosis in a large US cohort of over 1,500 cases

Authors: Gorlova O et al; presented by M Mayes, University of Texas, Houston, Texas

Summary: This large genome-wide association study used the Ilumina 550k gene chip to assess the genetic component of systemic sclerosis (SSc) risk in data from 1534 Caucasian cases compared with 3597 Caucasian controls. Thirty-three single-nucleotide polymorphisms (SNPs) representing 12 genes were significantly associated with SSc, with p values from 9.9×10^{-15} to 5×10^{-8}. The most significantly associated genes were those in the MHC region (6p21), including, but not limited to, HLA-Class II alleles. In addition to the MHC region, four gene regions were identified as significantly associated with SSc: *TNPO3* ($p=1.2\times10^{-9}$ for the most significant SNP), noted by the study authors to be in linkage disequilibrium with *IRF5* and previously associated with SSc in candidate gene studies; *XKR4* on chromosome 8 ($p=5.15\times10^{-9}$); *TSSC1* on chromosome 2 ($p=2.53\times10^{-9}$); and *TUBA3C* (tubulin-α 3c) on chromosome 13 ($p=3.73\times10^{-8}$). P values for T-cell signalling-related genes (*CD3Z*, 2.37×10^{-6}), cytokine receptors (*IL21R*) and other previously studied candidate loci were in the range of 10^{-7} to 10^{-6}.

Comment: A GWAS in scleroderma patients revealed three SNPs in 12 different genes, the majority of which were in the MHC region but not restricted to Class II. The four non-MHC SNPs included one that is in linkage disequilibrium with interferon 5, but none of these is specific for scleroderma. This study confirms a role for autoimmunity in this disease and demonstrated considerable heterogeneity in keeping with the clinical picture.

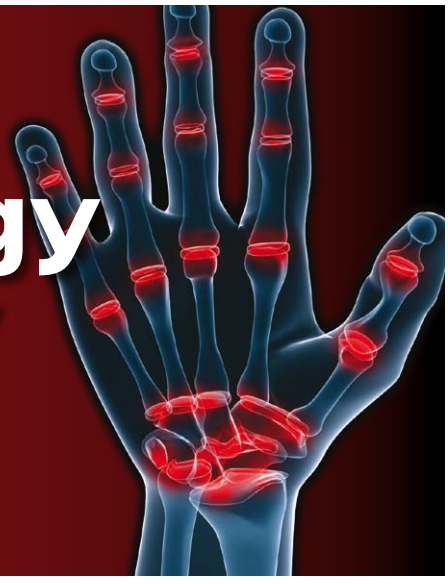
Abstract Session: Plenary Session I: Discovery 2009; Presentation 548

http://acr.confex.com/acr/2009/webprogram/Paper10863.html

Investigating lower back pain

Richard Deyo from Portland Oregon presented a Clinical Symposium on lower back pain that focused on assessment and management of mechanical causes, with the following key messages.

- A specific diagnosis can be made in only 10% of cases.
- Evaluation is required to rule out systemic causes and to identify surgical candidates.
- Neoplasms are effectively never found in patients who do not have historical risk factors.
- There is a high prevalence of asymptomatic MRI pathology, especially over the age of 60 years.
- Rates of surgical intervention correlate with availability of MRI.
- Randomisation to MRI as opposed to plain film x-ray increased the rate of surgery, but did not improve outcomes.
- Use of epidural injection of corticosteroid is on the rise, but this is only effective (modestly and temporarily) when there is radiculopathy.
- There is poor quality evidence for opioids and some evidence of harm from long-term use.
- Exercise is the mainstay for chronic pain, with good evidence supporting tricyclics and multidisciplinary pain services.
- Surgery should only be considered when the clinical picture and imaging are in agreement.



Highlights of the concurrent session – 'Rheumatoid Arthritis Therapy: Biological Therapy'

Smoking is associated with non-response to methotrexate and to anti-TNF treatment in patients with rheumatoid arthritis: results from the Swedish EIRA study

Authors: Saevarsdottir S et al; presented by Saedis Saevarsdottir, Karolinska University Hospital, Stockholm

Summary/comment: Data on treatment response rates in rheumatoid arthritis (RA) were sourced from a population-based survey and the Swedish Biologics Register. Nonresponse was defined as failure to improve 0.6 DAS28 units or a DAS >5.8. For methotrexate (MTX) treatment, 40% of current smokers and 28% of never smokers were nonresponders (OR 1.8 [95% CI 1.2, 2.7]) without a clear pack-year dose response. For anti-TNF therapy, 40% of current smokers and 25% of never smokers were nonresponders (OR 2.0 [95% CI 1.1, 3.7]) independent of concurrent MTX use and exhibiting a pack-year dose response. Female gender also predicted nonresponse, but serology and shared epitope status did not. A history of previous, but not current, smoking did not predict nonresponse to either MTX or TNF inhibitors. This study provides further evidence for a need to encourage smoking cessation in patients with RA.

Abstract Session: ACR Concurrent Abstract Sessions; Rheumatoid Arthritis Therapy: Biological Therapy; Presentation 635

http://acr.confex.com/acr/2009/webprogram/Paper15312.html

Rituximab in combination with MTX significantly inhibits joint damage and improves clinical outcomes in patients with early active RA who are naïve to MTX: a randomized active comparator placebo-controlled trial (IMAGE)

Authors: Tak PP et al; presented by Paul P Tak, Academic Medical Center/ University of Amsterdam, Amsterdam

Summary/comment: This 52-week trial compared clinical responses and erosive progression in RA patients, all of whom received MTX and who were randomised to either rituximab (RTX) 2 × 500mg, 2 × 1000mg or placebo. Erosions at baseline were required for inclusion. Whereas both doses of RTX gave similar clinical responses that were significantly superior to MTX alone, only the higher dose of RTX gave a significant reduction in radiographic progression compared with MTX alone. These data suggest that the lower dose of RTX may be suitable for the control of clinical measures of outcome but also indicate that the 2 x 1000 mg dose may be required to optimise radiographic outcome.

Abstract Session: ACR Concurrent Abstract Sessions; Rheumatoid Arthritis Therapy: Biological Therapy; Presentation 636

http://acr.confex.com/acr/2009/webprogram/Paper14716.html

LITHE: tocilizumab inhibits radiographic progression and improves physical function in RA patients at 2 yrs with increasing clinical efficacy over time

Authors: Fleischmann R et al; presented by Roy Fleischmann, Metroplex Clinical Research Center, Dallas, Texas

Summary/comment: LITHE is a randomised trial of tocilizumab (TCZ) 4mg or 8mg or placebo every 4 weeks in RA patients receiving MTX. Patients with <70% improvement in tender and swollen joint count at 52 weeks were switched to TCZ 8mg for the second year. Because of the escalation, there was no significant difference in clinical measures at the end of year 2, but the 8mg group had 81% less progression and the 4mg group had 74% less progression than the MTX-only controls. Adverse events leading to withdrawal were higher in the TCZ groups, but there was no difference in serious adverse events between the groups. TCZ plus MTX is significantly more effective at preventing radiographic progression than MTX alone.

Abstract Session: ACR Concurrent Abstract Sessions; Rheumatoid Arthritis Therapy: Biological Therapy; Presentation 637

http://acr.confex.com/acr/2009/webprogram/Paper15221.html

Other highlights

Also presented at this session were the 2-year data from the AGREE trial that compared abatacept (ABA) plus MTX with MTX alone in early RA. All patients received ABA and MTX in the second year. 55% of patients in the ABA year 1 and 2 group achieved remission versus 44.5% in the ABA for year 2 only group. Nonprogression of erosions was seen in 56.8% of the ABA year 1 and 2 group, versus 43.8% in the ABA year 2 only group, the differences in both cases being significant.

Paul Emery presented radiographic data from the GO-BEFORE (MTX-naïve patients; n=637) and GO-FORWARD (MTX-inadequately responding) trials of golimumab (GLM). Both the 50mg + MTX and 100mg + MTX doses of GLM inhibited radiographic progression in the MTX-naïve study compared with MTX alone. In contrast, there was no difference in radiographic progression between the GLM + MTX and MTX alone groups, which the presenter attributed to the minimally progressive status of this late RA population.

Resolution of inflammation following treatment of ankylosing spondylitis with anti-TNF agents is associated with new bone formation

Authors: Chiowchanwisawakit P et al; presented by Walter P Maksymowych, University of Alberta, Edmonton, Alberta

Summary/comment: This study examined the validity of the 'release of TNF brake' hypothesis that TNF inhibition results in new bone formation by downregulating Dickkopf-1. Twenty eight patients receiving TNF inhibitors and 23 patients receiving 'standard therapy' were followed over a mean of 18 months with MRI scans at the beginning and end of the study. In the patients receiving TNF inhibitors, there was significantly more new syndesmophyte formation at the sites of resolving vertebral corner inflammatory lesions than there was at persisting vertebral corner inflammatory lesions. This was not observed in patients receiving standard therapy. This study supports the hypothesis that inhibition of TNF within localised inflammatory lesions results in new bone formation by release of the 'TNF brake'.

Abstract Session: ACR Concurrent Abstract Sessions: Spondyloarthritis: Treatment; Presentation 1257

http://acr.confex.com/acr/2009/webprogram/Paper11910.html

New Zealanders at the ACR

The growing contribution of NZ researchers to the understanding of gout was evident at the 75th ACR. In the first of her two oral presentations, Nicola Dalbeth (Auckland) presented evidence that skim milk has a urate-lowering effect; supporting Choy's observation that risk of gout was negatively correlated with dietary intake of dairy products. In her second presentation, she showed data characterising inflammatory cell phenotypes and cytokine profiles in gouty tophi. Lisa Stamp (Christchurch) presented a study of gout patients whose dose of allopurinol was safely and effectively escalated above the dose recommended by Hande criteria. Tony Merriman (Dunedin) was given a 'notable poster' award (top 15%) for his work that confirmed a role for the *ABCG2* gene in Western, but not Eastern, Polynesian patients with gout.

Highlights of the Plenary Sessions, 'Discovery 2009'

Rituximab versus cyclophosphamide for induction of remission in ANCA-associated vasculitis: a randomized controlled trial (RAVE)

Authors: Stone JH et al; presented by U Specks, Mayo Clinic, Rochester, Minnesota

Summary/comment: Patients with severe ANCA-positive Wegener's granulomatosis or microscopic polyangiitis were randomised to receive either rituximab (RTX; n=99) or oral cyclophosphamide (CYC; n=98). The primary endpoint of steroid-free remission was achieved in 63 patients in the RTX arm versus 52 in the CYC arm. The secondary endpoint of remission on prednisone <10 mg/day was achieved in 70 of the RTX-treated patients versus 61 in the CYC group. In both cases, this represents noninferiority rather than superiority, although subgroup analysis showed superiority for RTX in patients presenting in severe flare. Responses in patients with renal involvement or alveolar haemorrhage were similar. The presenter suggested that RTX should be considered in patients with ANCA-associated vasculitis, particularly when there are concerns about potential gonadal toxicity.

Abstract Session: Plenary Session I: Discovery 2009; Presentation 550

http://acr.confex.com/acr/2009/webprogram/Paper11655.html

Azathioprine versus mycophenolate mofetil for maintenance immunosuppression of proliferative lupus nephritis: results of a randomized trial (MAINTAIN)

Authors: Houssiau FA et al; presented by Frederic A Houssiau, Universite catholique Louvain, Brussels

Summary: This is a randomised trial of mycophenolate mofetil versus azathioprine as maintenance therapy in patients with active lupus nephritis (LN) who had undergone the Euro-Lupus regimen of 6 × fortnightly pulsed IV cyclophosphamide and methylprednisolone. Approximately 50 patients in each group were followed over a median of 53 months. Mycophenolate mofetil was was not superior to azathioprine for preventing renal flare of lupus.

Abstract Session: Plenary Session II: Discovery 2009; Presentation 1150

http://acr.confex.com/acr/2009/webprogram/Paper13546.html

Efficacy and safety of rituximab in subjects with active proliferative lupus nephritis (LN): results from the randomized, double-blind phase III LUNAR study

Authors: Furie R et al; presented by R Furie, North Shore-LIJ Health System, Lake Success, New York

Summary: This study examined whether the addition of RTX provided any advantage in patients undergoing treatment with mycophenolate mofetil and corticosteroids for proliferative LN. There was no difference between the RTX and placebo groups in achieving the endpoints of complete or partial renal remission. It was felt that the high response rate to background therapy may have contributed to the failure to demonstrate superiority.

Abstract Session: Plenary Session II: Discovery 2009; Presentation 1149

http://acr.confex.com/acr/2009/webprogram/Paper12419.html

Comment: Taking these two studies together, it might be concluded that IV cyclophosphamide followed by azathioprine is a reasonable treatment option for renal lupus unless cyclophosphamide is contraindicated for ovarian reasons, in which case mycophenolate mofetil is the treatment of choice. The role of RTX is yet to be proven.

Combination antibiotics as a treatment for chronic *Chlamydia*-induced reactive arthritis

Authors: Carter JD et al; presented by John D Carter, University of South Florida, Tampa, Florida

Summary/comment: This is an RCT of doxycycline and rifampicin versus azithromycin and rifampicin versus placebo in patients with reactive arthritis (ESSG criteria +ve) who were PCR positive for *Chlamydia trachomatis* or *C. pneumoniae*. The groups given combination antibiotics showed significant improvements in the outcome measures compared with placebo. After 6 months, 6/27 in the antibiotic group had complete resolution versus 0/15 in the placebo group. The authors believe that the failure of previous studies of antibiotic therapy is a reflection of the need for a combination approach to eradicate the viable organisms.

Abstract Session: Plenary Session II: Discovery 2009; Presentation 1152

http://acr.confex.com/acr/2009/webprogram/Paper14878.html

Toll-like receptor 4 blockade ameliorates murine and humanized models of RA: a comparison with IL-1 and TNF blockade

Authors: Abdollahi-Roodsaz S et al; presented by Shahla Abdollahi-Roodsaz, Radboud University Nijmegen Medical Centre, Nijmegen

Summary/comment: Toll-like receptors (TLRs) have been proposed as potential targets for treatment of inflammatory disease. This study investigated the effect of TLR4 blockade in established collagen-induced arthritis in mice and in severe combined immunodeficiency (SCID) mice engrafted with active RA synovial tissue. In these models, TLR4 blockade using *Bartonella quintana* lipopolysaccharide was as effective as etanercept (Enbrel) and anakinra in suppressing collagen-induced arthritis, including cartilage pathology. TLR4 blockade, but not TNF or IL-1 blockade, decreased synovial and serum levels of IL-17. TLR4 blockade suppressed cytokine production in SCID mice engrafted with RA synovial tissue to the same extent as TNF blockade, whereas IL-1 inhibition had no effect. This study indicates that TLR4 stimulation is upstream of currently utilised targets in inflammatory arthritis and suggests that TLR4 inhibition may have therapeutic potential.

Abstract Session: Plenary Session III: Discovery 2009; Presentation 1897

http://acr.confex.com/acr/2009/webprogram/Paper15858.html

TEAR: treatment of early aggressive RA; a randomized, double-blind, 2-year trial comparing immediate triple DMARD versus MTX plus etanercept to step-up from initial MTX monotherapy

Authors: Moreland LW et al; presented by Larry W Moreland, University of Pittsburgh, Pittsburgh, Pennsylvania

Summary/comment: This RCT divided 755 active early RA patients into 4 arms: 1) immediate MTX + etanercept; 2) immediate triple DMARD therapy (MTX/SSZ/HCQ); 3) step up from MTX to MTX + etanercept; and 4) step up from MTX to triple therapy; the step up was made at 6 months in groups 3 and 4 if the DAS28 was >3.2. At 6 months, the immediate therapy groups had significantly better ACR responses than the step-up groups who had been receiving MTX alone, but there was no significant difference between groups 1 and 2. There was no significant difference in DAS scores between any of the groups at 2 years as a result of the poor responder step up at 6 months. This study questions the need for TNF inhibitors ahead of combination DMARDs in early RA. It also contradicts the mantra of certain senior European 'speaking circuit' rheumatologists that combination DMARDs are of no value in RA.

Abstract Session: Plenary Session III: Discovery 2009; Presentation 1895

http://acr.confex.com/acr/2009/webprogram/Paper13099.html

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