American College of Rheumatology

Conference Review

Making Education Easy 74th ACR Annual Scientific Meeting, 6–11 Nov 2010, Atlanta, Georgia, USA

In this issue:

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Welcome

to our review of the 74th ACR Annual Scientific Meeting, a locally focused summary of some of the latest and most exciting developments in rheumatology research presented at the 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 Atlanta, USA. The abstracts presented at the meeting can be accessed from http://www.abstracts2view.com/acr/.

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

Kind regards,

Dr Chris Tofield
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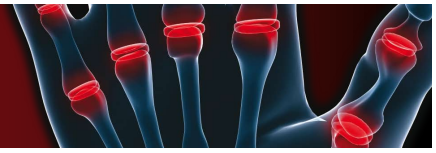
The great debate: is it time to use biologicals as first-line therapy in rheumatoid arthritis?

Daniel Furst presented the case for the affirmative, arguing that the data demonstrate long-term benefits from early induction of remission, a state more readily achieved with biological therapies than with traditional disease-modifying antirheumatic drugs (DMARDs). James O'Dell, a veteran investigator of combination DMARD regimens, was an appropriate choice to represent the negative, highlighting the decades of data demonstrating the benefits of methotrexate and other oral agents, with particular reference to the cost effectiveness of first-line oral DMARD therapy. While no-one denies a role for biological therapies in the management of rheumatoid arthritis (RA), a major controversy in this area is the timing of the introduction of these agents – a parameter that greatly influences the cost-benefit analysis. Ultimately, the regulations provided by health funders serve as a firm framework on which these decisions are made, but prescriber behaviour can significantly influence the speed with which the patient progresses to a biological agent. At the end of the session, the issue remained unresolved.

Scleroderma

Scleroderma was a strong theme at the 2010 ACR. The state-of-the-art lecture by John Varga from Chicago outlined the relationship between inflammation, autoimmunity, fibrosis and vasculopathy, and developed a hypothesis for the pathogenesis of scleroderma involving roles for: i) TLR3 and TLR4 as immune-recognition signalling mediators of fibrosis; ii) TGF-β as tissue damage-derived proinflammatory cytokine; iii) egr-1 as an important component of signal transduction for fibrogenesis; and iv) PPAR-γ as a nuclear receptor and transcription factor that downregulates fibrosis.

Highlights of other scleroderma sessions included the demonstration that HLA-DRB1*0407 and *1304 are independent risk factors of scleroderma renal crisis,[1] and a study that found gastric antral vascular ectasia (GAVE), not predicted by haemoglobin levels, in 22% of patients screened endoscopically.[2] It was suggested that scleroderma patients undergoing treatment with cyclophosphamide should be screened for GAVE in case thrombocytopenia should develop, increasing the risk of bleeding.



The results of a trial of mycophenolate mofetil for cutaneous scleroderma were presented,[3] and there seemed to be a modest benefit, although the use of historical controls from other studies was a limitation of the study. An open-label trial was presented showing an improvement in skin score and FVC associated with use of imatinib.[4] Although neither study was randomised and the imatinib study was uncontrolled, these agents may be worthy of further evaluation.

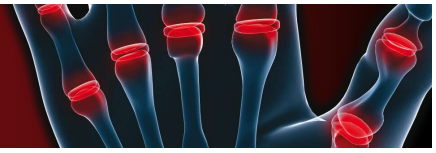
In a clinical symposium on new approaches to therapy for scleroderma, Richard Silver (South Carolina) summarised the existing, current and planned trials for treatments of scleroderma lung disease. There is some evidence of benefit for cyclophosphamide, but he described other agents such as colchicine, interferon-γ-1b, imatinib, etanercept and bosentan as ineffective. A trial of mycophenolate mofetil is currently in the recruitment phase. Trials of thalidomide and a tyrosine kinase inhibitor, as well as other treatments targeting various cytokines and growth factors, are planned or underway.

Frederick Wigley (Johns Hopkins) outlined the current treatments for peripheral and pulmonary vasculopathy in scleroderma. His approach to the management of digital ischaemia includes avoidance of aggravating factors (cold, smoking, etc), use of calcium channel blockers, followed by the addition of a phosphodiesterase inhibitor, nitrates or prostaglandins, and then a vasoprotective agent like a statin, for which there is some evidence of benefit, or bosentan. The place for imatinib, *N*-acetylcysteine and sympathectomy were also discussed.

Alan Tyndall (Basel) presented the rationale for, and experience of, the use of autologous stem-cell transplantation and mesenchymal stem-cell therapy in the treatment of scleroderma, both of which promise benefit, but for which the risks, costs and current lack of RCT evidence surely limit widespread application.

Abstracts

1. ***Nguyen BY et al. HLA DRB1*0407 and *1304 are predictive biomarkers for scleroderma renal crisis; abstract 725***
2. ***Hung EW et al. GAVE (gastric antral vascular ectasia) in early diffuse SSc: updated report from the SCOT (Scleroderma Cyclophosphamide or Transplant) trial; abstract 726***
3. ***Le E et al. Long-term benefit of mycophenolate mofetil for treatment of diffuse cutaneous systemic sclerosis; abstract 2192***
4. ***Spiera RF et al. Imatinib mesylate (Gleevec™) in the treatment of diffuse cutaneous systemic sclerosis: results of a one year, phase IIa, single arm, open label clinical trial; abstract 2193***



Wegener's granulomatosis and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis

This area was well represented at the 2010 meeting, with a clinical symposium outlining the trial data and an oral abstract session dedicated to ANCA-associated vasculitis (AAV).

The trials of conventional immunosuppressive agents (cyclophosphamide, methotrexate, azathioprine and mycophenolate mofetil) were reviewed by Dr Philip Seo of the Johns Hopkins Vasculitis Center, and the take home messages were that:

i) cyclophosphamide is effective, but associated with significant toxicity

ii) methotrexate is effective in inducing remission in milder disease, but associated with more relapses

ii) azathioprine and methotrexate, and to a lesser extent mycophenolate mofetil, can help maintain remission after cyclophosphamide

iv) pulsed IV cyclophosphamide is not inferior to continuous daily oral treatment.

Dr Ulrich Specks of the Mayo Clinic then reviewed trials of biological agents in Wegener's/MPA. The take home messages were that:

i) etanercept does not add benefit to standard therapy and increases the risk of malignancy (WGET trial)

ii) rituximab is not inferior to cyclophosphamide in AAV, even with renal and alveolar disease, and may be superior to cyclophosphamide for patients in severe flare (RAVE trial)

iii) rituximab is not inferior to cyclophosphamide followed by azathioprine over 12 months (RITUXVAS trial)

iv) rituximab should be considered when preservation of fertility is important.

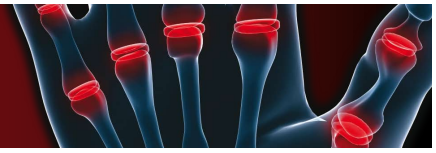
In the oral abstract sessions, follow-up data from the RITUXVAS study confirmed noninferiority of rituximab out to 2 years,[1] and the same group presented the results of another trial that showed that 6 monthly infusion of rituximab 1 × 1g was associated with fewer relapses and earlier withdrawal of immunosuppressive treatment than rituximab reinfused at flare in AAV patients in whom remission had been induced with rituximab 2 × 1g.[2]

Abstracts

1. ***Jones RB et al. Two year follow-up results from a randomised trial of rituximab versus cyclophosphamide for 'generalized' ANCA-associated vasculitis: RITUXVAS; abstract 676***
2. ***Jones RB et al. Protocolised versus non-protocolised rituximab treatment for refractory ANCA-associated vasculitis; abstract 678***

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.



The preclinical stage of RA: towards prevention of disease?

One of the most exciting recent discoveries in RA has been the elucidation of the link between environmental factors, such as cigarette smoking, genetic factors, including the shared epitope, and the development of an immune response against citrullinated peptides that results in autoimmune disease in joints and other tissues. In this session, Lars Klareskog of the Karolinska Institute began by demonstrating that this autoimmune response may begin as early as 10 years before the onset of clinical disease. He summarised the data showing that cigarette smoke-induced citrullination only leads to anticitrullinated protein antibody (ACPA)-positive RA in the presence of the shared epitope. Nonsmokers who possess the shared epitope needn't be too smug; other environmental triggers such as *P. gingivalis*-induced citrullination of enolase have been documented, and citrullinated enolase and other ACPA targets have been found in the synovium. A role for T-cells was demonstrated; the ACPA interactions are predominantly HLA-DR4 and HLA-DRB1*04 restricted, and a role for the lymphocyte activation gene *PTPN22* in smokers has been shown. In fact, there are many different ACPAs reactive with a range of different citrullinated peptides, and these can result from various gene-environment interactions. Klareskog hypothesises that a "cure" for RA could result from an intervention in the preclinical or minimally symptomatic early stages of RA, whereas interventions once inflammation has become evident could only be expected to control the disease at best.

Hani El-Gabalawy from the University of Manitoba presented data from a study of North American Natives with a high prevalence of RA in which multi-case families are common and the prevalence of rheumatoid factor (RF) and ACPA is high (around 90%). The differences in ACPA specificities between RA cases and healthy seropositive individuals suggest that isotope expansion and epitope spreading are mechanisms leading to development of disease.

Daniëlle M Gerlag from the University of Amsterdam discussed the evidence that chronic synovitis is present in the preclinical phase of RA, and indicated that a study of rituximab in individuals who are at high risk of developing RA, the PRAIRI study (Prevention of RA by Rituximab), is currently being conducted. A single infusion of rituximab 1000mg will be administered in the preclinical stages of disease, and follow-up will be over 4 years.

With a better understanding of the immunopathogenesis of early RA, the serological assays to identify individuals who are at high risk of progressing to clinical synovitis, the resolve to treat early and aggressively, and the drugs to switch off the immunogenic mechanisms, the possibility of curing RA does not seem too far from our grasp.

RA treatment - small molecules, biologicals and gene therapy: existing biologicals

In countries in which numerous biological therapies with a range of specific targets are available, decisions about the sequence of use of these agents can exercise the judgement of the modern rheumatologist. Should patients who have failed a tumour necrosis factor (TNF) inhibitor be prescribed a second TNF inhibitor or change to a treatment with a different molecular target? In the absence of randomised trials, meta-analyses of clinical trials can provide some insights. A meta-regression was presented that examined the comparative efficacy of biological treatments in patients with RA who failed first-line anti-TNF therapy.[1] The study compared ACR20, ACR50, and ACR70 response rates for biological therapies: second-line anti-TNF (adalimumab, certolizumab pegol, etanercept, golimumab or infliximab), anakinra, abatacept, rituximab and tocilizumab, in combination with methotrexate, in TNF-inhibitor failures. Regardless of whether trials in early disease were included in the analysis, patients switching to a second TNF inhibitor achieved ACR responses that were at least as good as rituximab and tocilizumab, and in all analyses there was a tendency for superiority over anakinra and abatacept. After acknowledging the limitations of the methodology and disclosing their links with industry, the authors concluded that a second TNF inhibitor should be considered for patients failing anti-TNF therapy.

Abstract

1. Benedict A et al. Comparative effectiveness of biologic therapies for treating rheumatoid arthritis (RA) in patients who failed an anti–tumor necrosis factor agent: a meta-regression analysis; abstract 2266

New Zealanders at the ACR

A strong contingent of New Zealanders attended the Atlanta ACR, presenting work from ongoing research programmes, including: i) abstracts on erosions and bone remodelling in psoriatic arthritis from a group led by Fiona McQueen; ii) abstracts on erosions an outcomes in gout from a group led by Nicola Dalbeth; and iii) abstracts from Paul Hessian's collaboration with Lisa Stamp, John Highton and others on the IL-23/IL-17A pathway and on dendritic cells in RA. Lisa Stamp presented some of her work on methotrexate pharmacokinetics and on myeloperoxidase in gout from her collaboration with Tony Kettle. And, a special mention for my PhD student, Valerie Milne, who was awarded an ACR Notable Poster Award for one of our abstracts on social and geographical barriers to rheumatology services.

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