European League Against Rheumatism Congress 2011

Conference Review

Making Education Easy

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In this review:

Independent commentary by Simon Stebbings

Simon Stebbings qualified from University College London. He is a Consultant Rheumatologist at Dunedin Hospital and a Senior Lecturer at Dunedin School of Medicine, University of Otago. His research interests include the pathogenesis of ankylosing spondylitis and the development of outcome measures in rheumatic disease. Dr Stebbings provides expert commentary for Rheumatology Research Review.

Independent commentary by Andrew Harrison

Dr Andrew Harrison is Clinical Head of the Wellington Regional Rheumatology Unit and Senior Lecturer in Medicine at the University of Otago Wellington. He is an Otago graduate and obtained his PhD from the Royal Postgraduate Medical School in London. His research interests include the basic cellular and molecular mechanisms of inflammation, the genetics of gout and rheumatoid arthritis, and access to healthcare resources. Dr Andrew Harrison provides expert commentary for Rheumatology Research Review.

Welcome to our review of the European League Against Rheumatism (EULAR) Congress 2011.

The review is a locally focussed summary of some of the latest and most exciting developments in rheumatic disease research presented at the conference, and it has been created to allow those unable to attend, but with a keen professional interest, to access a summary of some of the presentations. Review and commentary of the presentations/posters has been carried out by Simon Stebbings and Andrew Harrison who attended the meeting in London.

Abstracts from the meeting can be accessed via http://www.abstracts2view.com/eular/index.php.

We hope you enjoy this review of these presentations from the 2011 EULAR Congress.

Kind regards,

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Reviewer: Simon Stebbings

Treatment of spondyloarthritis

Whilst antitumour necrosis factor (anti-TNF) therapies have proved life-changing for many patients with spondyloarthritis, alternative therapies are needed for those who have mild disease, where the cost effectiveness of biological therapy is an issue, or who have a poor response to anti-TNF therapy or contraindications. This session presented data on a range of potential alternative therapies.

The anti-IL-17A monoclonal antibody secukinumab (AIN457) showed good safety and efficacy in the treatment of active ankylosing spondylitis

Secukinumab is a new anti-IL-17A monoclonal antibody therapy. The Th17 pathway is known to be a major component of the immune response in spondyloarthropathies.

Secukinumab was given as two infusions 3 weeks apart at a dose of 10 mg/kg; the half-life is 28 days. In the phase IIb study, 30 patients were enrolled with ankylosing spondylitis. Patients had high disease activity (mean BASDAI score 7.1). In total 24 patients completed the trial.

There was a rapid response to therapy after the first infusion. A Bayesian statistical analysis was used, which allowed a smaller placebo group to be used and historical controls from previous studies. In treated patients, ASAS20 responses were 61% with secukinumab versus 17% in the placebo group, indicating a probability of positive treatment difference of 99.8%. Serious adverse events were recorded – increased blood pressure (n=1) and subcutaneous abscess of the foot requiring drainage (n=1), both suspected to be study drug related. There were 17 cases of upper respiratory infections in the treated group, all assessed as mild.

Secukinumab may be useful for the treatment of active ankylosing spondylitis. Further studies of safety and efficacy can be expected.

Oral presentation 0174

The effect of alendronate on ankylosing spondylitis; the results of the bisphosphonates in ankylosing spondylitis trial (BIAS)

Treatment options for mild-to-moderate ankylosing spondylitis (AS) are still largely limited to NSAIDs. A study by Maksymowych et al [Arthritis Rheum 2002;46(3):766–73] suggested that IV pamidronate may be an effective therapy for AS in high doses, although this finding has not be confirmed in subsequent studies.

In this double-blind randomised-controlled multicentre trial, 182 patients were randomised, and 92 received alendronate 70mg weekly and 88 received placebo for 2 years patients; 148 completed the study.

There was no improvement in symptoms, disease activity or function when patients taking alendronate were compared with those on placebo, in contrast to some previous studies. However, most previous studies have been smaller, of shorter duration and with less well-defined AS. Alendronate does not have a role as a symptom- or disease-modifying drug in AS, but this finding may not necessarily translate to more potent IV bisphosphonates.

Oral presentation 0176

Tocilizumab in axial spondyloarthropathies: 18 cases

IL-6 is an important pro-inflammatory cytokine in ankylosing spondylitis (AS), and is a key driver of the C-reactive protein elevation seen in some patients with AS. Levels of IL-6 in the plasma correlate with the BASDAI. Therefore, tocilizumab has held promise as a potential therapy with translation to use in AS, just as anti-TNF agents have proven so effective in AS after their initial development to treat rheumatoid arthritis. Unfortunately, this interesting small observational cohort casts doubt on the potential for tocilizumab as a treatment in AS.

Although levels of C-reactive protein fell dramatically, as would be expected, a number of patients experienced an increase in pain and loss of function. BASDAI did not improve significantly, and only 25% of participants consented to continue after 10 months of treatment. It should be noted that the participants were an exceptional group, as all but one had failed anti-TNF therapy.

Oral presentation 0178

Are we sick of genetics?

Therapeutic targets and personalized medicines: the next ten years

Dr L R Cardon

Since the sequencing of the human genome, the potential for translating genetic research into therapies or more achievably influencing the choice of medication in an individual has been seen as achievable. There are probably around 4000 candidate alleles that may be potential targets for intervention. In most cases however, common genetic variants exert only a modest influence over disease severity or characteristics.

Targeting therapies by identifying drug responders and nonresponders is currently one successful use of genetic markers. This is most widely used in oncology (e.g. the presence or absence of HER2 in breast cancer). In macular degeneration, response to intravitreal injection with bevacizumab can now be predicted by the presence of genes coding for complement factor H. Another important area is the identification of individuals at risk of adverse events from specific medications, for example, SLC01B1 is associated with statin myopathy, HLA-B5701 with liver toxicity associated with flucloxacillin and abacavir. Such effects are usually the result of single genes with a high penetrance and significant effects on drug metabolism.

In the future, many further studies are likely to demonstrate translational utility of genetic testing. All such studies rely greatly on well-characterised and defined clinical entities.

Osteoporosis

Body mass index and bone mineral density: can we exclude a diagnosis of osteoporosis in obese patients without a DEXA scan?

DEXA scanning has become the gold standard for assessing risk of fracture. In NZ, it is hard to access funded medication for osteoporosis without a DEXA scan. However, can we save time and money by clinically stratifying patients to identify those who require DEXA?

In this large study, >10,000 patients were studied using a model to examine the effect of BMI on bone mineral density correcting for other risk factors such as age, gender, index of deprivation and clinical risk factors.

Obese patients referred for DEXA scanning had a lower prevalence of osteoporosis than the general population. It may be justified to forego DEXA scanning in patients with BMI >30 kg/m^2, particularly in patients aged <70 years with few other risk factors.

Oral presentation 0281

Enhanced expression of ephrins and thrombospondins in the dermis of patients with early diffuse systemic sclerosis

Ephrins are components of cell signalling pathways and essential regulators of angiogenesis. Thrombospondins are inhibitors of angiogenesis and strong promoters of fibrosis. Both are involved in the immunopathology of systemic sclerosis (SSc). In this study, skin biopsies from eight patients with SSc and four healthy volunteers were taken. Dermal fibroblasts were cultured, and ephrin (EphB4 and EphrinB2) and thrombospondin (TSP-1 and 2) mRNA and protein levels were analysed in skin tissue. Increased levels of EphrinB2 and EphB4 were detected in clinically involved skin of patients with SSc, and expression of ephrins was restricted to blood vessels. TSP-1 and 2 were upregulated in SSc skin biopsies taken from both involved and noninvolved skin, where expression was mainly in the extracellular matrix at the periphery of vessels. EphB4 and EphrinB2 upregulation suggests their participation in perturbations of angiogenesis seen in SSc. TSP-1 and 2 are upregulated in SSc dermal fibroblasts. Since these pathways are already being investigated as potential therapeutic targets in tumour angiogenesis, there is a possibility that drug repositioning may yield benefits in SSc.

Poster presentation FRI0418

Results from a genome-wide association study investigating psoriatic arthritis susceptibility loci

Genotype data from 492 patients in the UK with psoriatic arthritis (PsA; cases) and 5984 healthy controls were analysed with control data from the Wellcome trust database (WTCCC2). An analysis confirmed associations previously identified for PsA risk loci, notably HLA-C, IL12B, IL23R and TRAF3IP2. In addition, other loci associated with skin psoriasis, but not previously associated with PsA, were identified: IL28RA, TNIP1, IL23A and RNF114. With the exception of IL-23R, PsA seems to show a different pattern of genetic susceptibility to other forms of spondyloarthritis.

Poster presentation THU0088

Reviewer: Andrew Harrison

JAK inhibitors

There were numerous presentations on trials of Janus kinase (JAK) inhibitors in rheumatoid arthritis (RA), particularly tofacitinib, tasocitinib and fostamatinib. Joel Kramer summarised the data from the phase II and III trials of tofacitinib in the *Update in RA therapeutics: targeting intracellular signalling* session. The phase II trials of tofacitinib determined that the 5mg twice daily and 10mg twice daily dosages would be studied in phase III. These trials have shown superior efficacy over placebo with ACR20, 50 and 70 responses of 58.7–70.5%, 44%, and 24.6–30.7%, respectively, at 12–24 weeks. Side effects included infection, raised aminotransferase levels, raised LDL cholesterol levels, anaemia, neutropenia and raised serum creatinine levels. New data from phase III trials of this drug were presented, including a late-breaking abstract from Joel Kramer et al that showed that adding tofacitinib is superior to placebo in patients with active disease, despite conventional DMARDs. There was a small increase in discontinuation due to adverse effects at 6 months in the treatment group (4.7%) compared with placebo (1.9%).

Fleischmann presented a subgroup analysis from a monotherapy study of tofacitinib in patients with RA not responding to DMARDs that showed ACR20 responses compared with placebo, regardless of serological status, age, weight, sex and prior biological use. There were trends toward better responses in younger, leaner, RF-positive and ACPA-positive patients.

A Korean study of another JAK inhibitor, tasocitinib, in 21 patients with RA was presented by J Kim. This showed promising reductions and even reversal of erosion scores in the treatment arm compared with conventional DMARDs. Weinblatt presented a study that showed improved health-related quality of life in patients with active RA receiving fostamatinib.

New treatments for gout

There has been considerable recent interest in IL-1 blockers in the treatment of gout. Evans presented a study of rilonacept during initiation of therapy with allopurinol 300mg daily without cover with NSAIDs or colchicine. Weekly injections of rilonacept reduced the number of flares and the number of days spent in flare. A multinational sister study with the same protocol presented by Mitha confirmed the results of the North American study, with a halving of gout flares in the treatment arms compared with placebo. Unfortunately, neither study included a 'current best practice' arm of slow stepwise increase of allopurinol under prophylactic cover, which I think PTAC would be interested in seeing before recommending funding.

There were numerous presentations of the same study of canakinumab, another IL-1 inhibitor, in acute gout unresponsive to, or intolerant of, NSAIDs or colchicine. Canakinumab was given as a single SC injection, with the lower than customary IM dose of triamcinolone (40 mg) as the comparator. Canakinumab was superior in relieving pain and reducing risk of new flares.

Lesinurad is a new uricosuric agent that blocks urate reabsorption in the proximal tubule by inhibiting URAT1, a renal urate transporter also inhibited by benzbromarone. Tan presented a study that examined the influence of thiazide diuretics on OAT4-mediated urate reabsorption, and which showed that lesinurad and benzbromarone had equipotent effects on OAT4 in blocking diuretic-mediated urate reabsorption. Studies were presented by Fleischmann and Perez-Ruiz that showed that lesinurad enhanced the urate-lowering effects of allopurinol and febuxostat. The difficulty in locating published evidence of lesinurad's effects as monotherapy suggests that this drug is not especially potent, hence the push to market it as adjunctive therapy in cases of failed xanthine oxidase inhibition.

Biosimilars

On the Thursday, there was a session devoted to biosimilars, a term used to distinguish the small molecule facsimiles that we refer to as generics from reproductions of biological therapies designed to be similar in structure and function to existing biologicals. This is of relevance in NZ, as we will be among the first countries to be allowed legal use of biosimilars once patents expire. The critical issue is that pharmacokinetic studies will not be sufficient for regulatory approval of these drugs; clinical trials will need to be conducted. Issues of affinity and selectivity are determined at a level that is not easy to predict or reproduce, due to the complex structure of biological molecules, especially antibodies.

OPTIMA study

Josef Smolen presented 78-week data from the OPTIMA study. Methotrexate (MTX)-naïve 'bad prognosis' rheumatoid arthritis patients with disease duration <1 year were randomised to receive adalimumab (ADA) plus MTX or placebo (PBO) plus MTX for 26 weeks, after which the ADA/MTX patients were randomised to withdraw ADA or continue to receive it for a further 52 weeks. MTX/PBO inadequate responders were given open-label ADA/MTX after week 26. At week 78, among those maintained on MTX alone, there were significantly more responders at the DAS28 <3.2 and 2.6 level and significantly less progression of erosions in the group that had received ADA for the first 26 weeks. PBO/MTX-inadequate responders who received ADA after week 26 had comparable clinical responses, but greater progression of erosions than those who received ADA in the first 26 weeks.

This study shows that a course of treatment with a TNF inhibitor in the first 26 weeks of disease provides better radiological outcomes than delaying anti-TNF treatment until MTX monotherapy has failed, and is consistent with the evolving notion that early aggressive suppression of inflammation provides lasting benefit long after step-down of therapy.

New Zealanders at EULAR

There was a large contingent of New Zealanders at EULAR this year, many of whom presented original research. Fiona McQueen was no stranger to the podium with two oral presentations, one on imaging in gout and the other on imaging of bone marrow oedema, which represents osteitis in the context of arthritis and which has been shown to be a precursor to bone erosion. Tony Merriman's group had five posters on gout genetics, one of which was selected for the poster tours, as was Lisa Stamp's poster on allopurinol hypersensitivity. Nicola Dalbeth had posters on the cellular basis of gouty erosions and the prevalence of gout, and Simon Stebbings presented a poster on the link between axial spondyloarthritis and the bowel.

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