European League Against Rheumatism
Conference Review

Making Education Easy

Annual European Congress of Rheumatology, June 2009, Copenhagen, Denmark

In this issue:

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

This Review has been created to allow those with a keen professional interest in rheumatology research to access a summary of significant clinical studies presented, which are likely to affect current practice. Selection and review of the research was carried out independently by Dr Hedley Griffiths, Barwon Rheumatology Services, who attended the EULAR Annual Scientific Meeting held in Copenhagen, Denmark.

Kind Regards,

Dr Janette Tenne-Brown
Medical Research Advisor
janette@researchreview.com.au

Inhibition of joint damage and improved clinical outcomes with a combination of rituximab (RTX) and methotrexate (MTX) in patients (PTS) with early active rheumatoid arthritis (RA) who are naive to MTX: a randomised active comparator placebo-controlled trial

Authors: Tak PP et al

Summary: 755 patients with early, active rheumatoid arthritis not previously treated with methotrexate were randomised to either placebo + methotrexate, rituximab (2 x 500mg) + methotrexate or rituximab (2 x 1000 mg) + methotrexate. Methotrexate was initiated in all groups at 7.5 mg/wk and titrated to 20 mg/wk by week 8. Rituximab was given by IV infusion on Days 1 and 15. At 52 weeks, compared with methotrexate alone, rituximab (2 x 1000 mg) + methotrexate produced a significantly lower change in Genant-modified total Sharp score and a higher proportion of patients with no joint progression according to radiological criteria. Clinical outcomes were improved with both doses of rituximab compared with methotrexate alone, including higher proportions of patients achieving ACR90 and major clinical response. Adverse events were consistent with known adverse effects of rituximab and methotrexate. The percentage of serious adverse events was similar across the 3 treatment groups, and the rate of serious infections was not significantly different between the groups. Three deaths were reported (pneumonia [2] and cerebral infarct), all in the methotrexate alone group.

Comment: This was a well constructed and well run study. It is reassuring to have data that supports the efficacy of this B-cell depletion therapy in rheumatoid arthritis. It remains unclear about what a reduction of one unit in the radiological scoring actually means in terms of long-term clinical impact. The study also demonstrated that methotrexate is a pretty effective agent in its own right, although not as potent as the combination of methotrexate plus rituximab.

Abstract Session: New aspects of B cell depletion for RA. Ann Rheum Dis. 2009;68:(Suppl 3):75

http://www.abstracts2view.com/eular/view.php?nu=EULAR09L_OP-0022

About the Reviewer -

Dr. Hedley Griffiths is a rheumatologist in a group private practice in Geelong, Barwon Rheumatology Service, who also works as a visiting specialist at Geelong Hospital. This private practice services Geelong, Ballarat, Warrnambool and St Helens in Tasmania. Dr. Griffiths is the current president of the Victorian branch of the ARA.

Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial (SIERRA)

Authors: Bingham CO et al

Summary: The Study Investigating the Effects of Rituximab on Rheumatoid Arthritis Patients (SIERRA) examined the effect of rituximab therapy on vaccine efficacy in 103 patients with RA already receiving methotrexate, who were randomised to receive rituximab in addition to methotrexate or to continue receiving methotrexate alone. At predetermined times, all patients received the tetanus toxoid adsorbed vaccine, the 23-valent pneumococcal polysaccharide vaccine (23VPPV) and neoantigen keyhole limpet hemocyanin (KLH), and the *Candida albicans* skin test. Serum IgG levels were measured prior to vaccine administration and 4 weeks later. Responses to tetanus vaccine were similar between the groups (39% of rituximab plus methotrexate recipients vs 42% of patients receiving methotrexate alone had a 4-fold rise in anti-tetanus IgG). The delayed-type hypersensitivity response to the *C. albicans* skin test was not affected by rituximab (77% vs 70% for methotrexate alone). However, rituximab did reduce responses to 23VPPV (57% vs 82%) and to KLH (47% vs 93%) compared with those on monotherapy.

Comment: I am not in the habit of deliberately immunising my patients prior to starting biological therapies, let alone DMARDs. This trial does not persuade me that I should change my habits as yet, but in high-risk individuals, such as the elderly, and those with airways disease, it would suggest that at least pneumococcal vaccine would be worth considering, and if required, it should be done before B-cell depletion therapy is commenced.

Abstract Session: New aspects of B cell depletion for RA. Ann Rheum Dis. 2009;68(Suppl 3):75.

http://tinyurl.com/mvp525

About Research Review

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Demyelinating diseases, optic neuritis, and multiple sclerosis in rheumatic diseases treated with anti-TNF-therapy

Authors: Fernández-Espartero MC et al

Summary: This study examined the incidence rates (IRs) of demyelinating disease, optic neuritis, and multiple sclerosis in patients with rheumatic diseases treated with tumour necrosis factor-alpha (TNF-α) antagonists, compared them with the IR in the general population and describes all cases communicated to the Spanish national drug registry, BIOBADASER. Up to September 2008, the registry included 9,256 rheumatic patients treated with biological treatments with an exposure of 21,425 patient-years. Of 49 patients with new-onset neurological signs and symptoms identified in BIOBADASER, 40 experienced neurological symptoms with the first TNF-α antagonist. In 32 patients, the treatment was discontinued. In 16 patients the outcome was reported as ''recovered". The diagnosis was confirmed in 9 cases of demyelinating disease, 5 cases of optic neuritis and 1 case of multiple sclerosis. When IRs in the general population were compared with the different anti-TNF-α drugs, multiple sclerosis rates were similar, but a higher rate of optic neuritis among recipients of anti-TNF-α drugs. No differences were seen between etanercept and infliximab, and there were no confirmed cases with adalimumab.

Comment: This was a report based on exploring a national drug database, involving over 21,000 patient-years. It underscores the importance of maintaining post-marketing surveillance for these new treatments, as it is only with time and maintaining vigilance through such instruments as national databases, that rare side-effects become apparent, despite their dramatic impact on rheumatoid disease. Because the anti-TNF drugs are so unique and "new", it is important for us as clinicians to maintain a level of caution in their use.

Abstract Session: Hot spots in rheumatic disease spectrum. Ann Rheum Dis. 2009;68:(Suppl 3):83.

http://www.abstracts2view.com/eular/view.php?nu=EULAR09L_OP-0045

Reduction of tophus size with pegloticase (PGL) in treatment failure gout (TFG): results from GOUT1 and GOUT2

Authors: Baraf HSB et al

Summary: Pooled data are reported from the replicate, 6-month, randomised, double-blind, placebo-controlled trials Gout Outcome and Urate Therapy 1 (GOUT1) and GOUT2 that examined the efficacy of IV pegloticase (8 mg q2w or q4w) in reducing tophus size in treatment failure gout. A total of 73% of patients enrolled in GOUT1 and GOUT2 (155/212) had ≥1 tophus at baseline. At the final visit, complete resolution of ≥1 tophus occurred in 40% q2w (p=0.002 vs placebo), 21% q4w (not significant vs placebo), and 7% placebo. Complete response (i.e. complete resolution of ≥1 tophus without any increase in size in any other tophus or appearance of new tophus) was higher in plasma urate responders (patients maintaining plasma urate <6 mg/dL for ≥80% of months 3 and 6) versus nonresponders (q2w, 62% vs 26%; q4w, 41% vs 11%). There were no plasma urate responders in the placebo group. Twenty-two percent of q2w subjects achieved CR in ≤13 weeks of treatment.

Comment: This report on two trials of pegloticase therapy for gout was well presented and clear. This treatment appears to be very effective in reducing the size and number of tophi, in a relatively short space of time (3–6 months), in a group of patients who would otherwise have no hope of effective therapy for their gout. It appears to be associated with the potential to exacerbate gout at the start of treatment, much the same as allopurinol and there appear to be some patients who do not respond to this treatment either. This report did not go into the side-effect profile. It would be a very useful alternative, if and when it becomes available in Australia.

Abstract Session: Hot spots in rheumatic disease spectrum. Ann Rheum Dis. 2009;68(Suppl 3):84.

http://www.abstracts2view.com/eular/view.php?nu=EULAR09L_OP-0047

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Defining remission in patients receiving tocilizumab is influenced by the choice of the composite index rather than by specific effects on the acute phase response

Authors: Aletaha D et al

Summary: Tocilizumab is known to have profound effects on the hepatic acute phase response (APR), but the relevance of APR improvement in the definition of remission (REM) and other disease activity states in rheumatoid arthritis (RA) is unclear. These researchers therefore compared composite indices with and without APR measures in 899 patients with active disease despite methotrexate or DMARD therapy, who were administered tocilizumab. At 6 months, remission rates as defined by the Disease Activity Score (DAS28), by the Simplified Disease Activity Index (SDAI), and by the Clinical Disease Activity Index (CDAI) were 30.0%, 7.9%, and 6.6%, respectively. Of patients in CDAI-REM, 95.0% and 98.3% were also in DAS28-REM or SDAI-REM, respectively; the remainder were all in the low disease activity (LDA) states of the respective other indices. In contrast, of patients in DAS28-REM or SDAI-REM, 20.7% and 81.7%, respectively, were also in CDAI-REM. Patients in DAS28-REM, but not CDAI-REM (79.3%), comprised mainly patients in CDAI-LDA (62.2%), but 16.7% were in CDAI-moderate disease activity (MDA), and 1 was in CDAI-high disease activity. In further analyses of the DAS28-REM group, the individual disease activity core variables of those who also attained CDAI-remission were compared with those who had CDAI-LDA or CDAI-MDA. All clinical variables were significantly higher in the CDAI-MDA group, whereas ESR decreased significantly in DAS28-REM patients with increasing levels of disease activity by the CDAI, thereby showing that even small changes in ESR can compensate for considerable clinical activity and disability.

Comment: Having only recently begun to regularly record the DAS28 on all of my rheumatoid patients, I was shocked to discover how many patients, who I thought were well controlled, still had a significantly elevated DAS score. This study provides an explanation for this discordance, at least in some patients. We all recognise patients whose disease would appear to be clinically well controlled but whose acute phase reactants remain elevated, for reasons that may not have anything to do with their rheumatoid disease. These are the patients in whom a DAS28 score may not give an accurate reflection of their true disease state because it heavily weights the ESR in its calculation. If we are to aim for a tight disease control in future, there may need to be some flexibility in the choice of index used to monitor individual patients.

Abstract Session: Novel therapeutic approaches for RA. Ann Rheum Dis. 2009;68(Suppl 3):123.

http://www.abstracts2view.com/eular/view.php?nu=EULAR09L_OP-0158

Baseline levels of CRP predict cardiovascular disease and arterial stiffness: results from the 15-year follow-up of the EURIDISS cohort

Authors: Provan SA et al

Summary: These researchers sought to determine whether early inflammatory markers of rheumatoid arthritis (RA) disease activity predicts cardiovascular disease (CVD) and levels of the augmentation index (AIx), a surrogate marker of cardiovascular disease, using 15 years of follow-up data from 108 EURIDISS study participants. At follow-up, 44 reported CVD. Among 102 patients with acceptable AIx recordings, baseline RA disease duration, hsCRP and scores of HAQ predicted both CVD and increased AIx after 15 years, in an adjusted univariate model ($p<0.05$ for all variables). In addition, the Ritchie index predicted CVD and use of methotrexate predicted increased AIx in adjusted univariate models. In the multivariate logistic model, disease duration and HAQ remained significant predictors of CVD, (Ritchie score remained in the model as a confounder of HAQ) ($p=0.02$, 0.06 and 0.53, respectively). Baseline CRP levels predicted AIx ($p=0.01$).

Comment: It is not often that one sees a study with 15 years of follow-up, but this report gives further weight to the need for controlling inflammatory disease in our patients, in order to minimise significant morbidity and mortality. It is increasingly apparent that uncontrolled inflammation, such as we see in rheumatoid arthritis, is one of the most potent risk factors for significant cardiovascular disease.

Abstract Session: Rheumatic diseases and cardiovascular comorbility. Ann Rheum Dis. 2009;68(Suppl 3):79.

http://www.abstracts2view.com/eular/view.php?nu=EULAR09L_OP-0033

Fever in the elderly – a rheumatologist's perspective

Authors: Hoffman GS

Summary: This review discusses the diagnostic challenge of fever presenting without localising signs and remaining without clear cause after 2–3 weeks of in-depth evaluation of evidence supporting the diagnosis of a viral infection. In cases of "fever of unknown origin" (FUO) only about 50% of adults are eventually diagnosed, whereas almost 90% of children are later diagnosed with proven infection. In adults aged >65 years, rheumatic diseases as a cause of FUO in general are more common and they more frequently experience infections and malignancies than younger age groups. The review notes that the spectrum of ultimate-diagnoses in FUO series has changed over the years, due to improved diagnostic tools leading to prompt diagnosis of many malignancies and infections and international travel exposing individuals to infectious diseases not commonly seen in developed countries (e.g. malaria, brucellosis, typhoid, kala azar, filariasis, schistosomiasis). The newer immunosuppressive therapies have heightened awareness among rheumatologists to fever in patients with already established autoimmune diseases who are predisposed to opportunistic infections.

Comment: This was an elegant dissertation on the difficulties and successes in diagnosing fevers of unknown origin, particularly in the elderly. In developed countries, autoimmune inflammatory diseases would appear to be rising in percentage terms as a cause for FUO in elderly patients, presumably because we are getting better at diagnosing and treating infections and cancer. In undeveloped countries, obviously infections remain the dominant cause for FUOs.

I was interested to learn that PET scanning appears to be on the rise as a useful tool in evaluating FUO patients, particularly for large vessel vasculitis. Biopsy to provide histology remains the corner stone in diagnosing vasculitis.

Abstract Session: Difficult vasculitis – Establishing the diagnosis. Ann Rheum Dis. 2009;68(Suppl 3):15.

http://tinyurl.com/nd2857

12 month safety and efficacy data of night time release prednisone: sustained reduction of morning stiffness and IL-6 combined with favourable safety profile for treatment in rheumatoid arthritis

Authors: Buttgereit F et al

Summary: Outcomes are reported from a 12-month clinical study involving 288 patients with active rheumatoid arthritis (RA), to investigate the safety and efficiacy of a modified-release (MR) oral formulation of prednisone. During study months 1–3, the MR tablet taken at bedtime was compared to immediate-release (IR) prednisone, taken in the morning. Prednisone doses were 3–10 mg/day. From months 4–12, all patients received MR prednisone at bedtime. During months 1–3, the mean relative reduction of morning stiffness duration was significantly higher with MR prednisone than with IR prednisone (22.7% vs 0.4%; $p<0.05$). At 12 months, the mean relative reduction of morning stiffness was 46.1% ($p<0.001$). In the initial 3-month phase, median interleukin (IL)-6 levels in the MR prednisone group decreased by 28.6% compared to zero in the IR prednisone group. However, during months 4–12, median IL-6 levels were reduced by a similar extent among patients in the former IR prednisone group who switched to the MR formulation. The reduction in IL-6 was maintained until study end. Adverse event incidence rates were low throughout the study and similar to known effects associated with low-dose glucocorticoid therapy.

Comment: This is a study of a novel and hopefully beneficial variation of a familiar and commonly used drug.

In this study, the comparator was a morning dose of prednisolone, but perhaps it should have been an evening dose of standard prednisolone, which in daily clinical practice is more effective at relieving early morning stiffness.

Perhaps we will be able to get away with a smaller dose of prednisolone because of increased efficacy through better timing of the plasma peak and possibly more effective IL-6 suppression.

Abstract Session: Non-biologic treatment of RA. Ann Rheum Dis. 2009;68(Suppl 3):133.

http://tinyurl.com/n3lafz

Functional outcomes from a phase II study of a novel P2X7 receptor antagonist, AZD9056, in patients with active rheumatoid arthritis (CREATE Study)

Authors: McInnes IB et al

Summary: This study assessed the effects of two doses of the novel $P2X_7$ antagonist, AZD9056, on physical function in patients with active rheumatoid arthritis (RA) receiving methotrexate and/or sulphasalazine. Patients were randomised to receive once-daily oral AZD9056 100 mg (n=24), AZD9056 400 mg (n=25) or matched placebo (n=26), for 4 weeks. Both doses of AZD9056 were associated with improvements in both American College of Rheumatology 20% (ACR20) response and Disease Activity Score in 28 joints (DAS28) score compared with placebo at Weeks 2 and 4. ACR20 was achieved at Week 2 by 9%, 25% and 45% of patients receiving placebo, AZD9056 100 mg and 400 mg, respectively; corresponding values at Week 4 were 27%, 40% and 65%, respectively. Furthermore, AZD9056 was associated with clinically meaningful improvements in mean overall health assessment questionnaire (HAQ) score and individual HAQ dimension scores.

Comment: Inhibitors of signalling pathways offer the benefits of a small molecule, which can be cheap to produce in comparison to biological agents and can be taken orally. The downside is that most signalling pathways have promiscuity of function and are therefore blocking such pathways that may lead to unwanted side-effects. In this small study, the severe adverse events were abdominal pain in one patient and raised ALT in another.

This study leads to improvement in clinical parameters but no change in acute phase reactants, possibly suggesting that the drug operates in the local environment of the joint, rather than systematically. We will be seeing more of this type of therapy in the future.

Abstract Session: Non-biologic treatment of RA. Ann Rheum Dis. 2009;68(Suppl 3):132.

http://www.abstracts2view.com/eular/view.php?nu=EULAR09L_OP-0182

Association of serum 1CTP and radiographic joint damage during treatment with low-dose prednisolone in early rheumatoid arthritis

Authors: Hafström I et al

Summary: The effects of low-dose prednisolone were examined on serum concentrations of bone remodelling markers in patients with early rheumatoid arthritis (RA) in relation to remission and radiological joint damage. Serum samples were analysed from 150 such patients at baseline, 3 and 12 months for the type I collagen telopeptide fragments CTX-1 and 1CTP. Seventy patients had received prednisolone 7.5 mg/day for 2 years, or no prednisolone (n=80), when they started with the first disease-modifying antirheumatic drug (DMARD). Low-dose prednisolone and disease remission were associated with reduction of 1CTP in serum, a reduction that significantly correlated with reduced radiographic joint damage as assessed by Sharp/van der Heijde scores. Patients in remission at 2 years had a larger reduction of 1CTP from baseline to 12 months than those not in remission, whereas the reduction of CTX-1 did not differ between remission groups.

Comment: Here we see further evidence to support the use of low-dose prednisolone early on in the treatment of active rheumatoid arthritis. Low-dose prednisolone, once again, is shown to have disease-modifying effects in rheumatoid disease.

Obviously, this does not provide evidence to use prednisolone without other disease-modifying therapy, but it does provide some reassurance for its use as an adjunct to other DMARDs.

Abstract Session: Non-biologic treatment of RA. Ann Rheum Dis 2009;68(Suppl 3):133.

http://www.abstracts2view.com/eular/view.php?nu=EULAR09L_OP-0186