EULAR Congress 2012
Conference Review

Making Education Easy

June 6–9, 2012; Berlin, Germany

In this review:

ABBREVIATIONS USED IN THIS REVIEW

CV = cardiovascular; **DAS** = Disease Activity Score; **DMARD** = disease-modifying antirheumatic drug; **HAQ** = Health Assessment Questionnaire; **IL** = interleukin; **MRP** = myeloid-related protein; **RA** = rheumatoid arthritis; **TNF** = tumour-necrosis factor.

Independent commentary by Associate Professor Andrew Harrison

Associate Professor 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. Associate Professor Andrew Harrison provides expert commentary for Rheumatology Research Review.

Welcome to this review of the European League Against Rheumatism (EULAR) Congress 2012

This Review has been created to allow those unable to attend, but with a keen professional interest in rheumatology, to access a summary of significant presentations at the conference. Review of the presentations has been carried out independently by Associate Professor Andrew Harrison who attended the EULAR Congress 2012 held June 6–9, 2012 in Berlin, Germany.

EULAR is the confederacy of European rheumatology associations, and its annual congress attracts 15,000 rheumatologists and allied health professionals from all over the world. Berlin provided a very agreeable backdrop to the 2012 EULAR meeting. If the take-home messages from the meeting could be put in one sentence, it would be something like 'regardless of how you achieve it, abrogation of inflammation will improve long-term outcomes and reduce the risk of CV disease and death'.

We hope you find this Conference Review stimulating, and we look forward to your feedback.

Kind regards,

Associate Professor Andrew Harrison
andrewharrison@researchreview.co.nz

LONG-TERM OUTCOMES OF MODERN TREATMENT

Use of anti-TNF therapy is associated with reduced cardiovascular event risk in rheumatoid arthritis

Authors: Nurmohamed MT et al

Summary: This analysis of data from adults with ≥2 RA diagnoses treated with ≥1 prescription of anti-TNF, methotrexate or other nonbiological DMARD therapy (48,621, 35,480 and 52,994 patient-years of follow-up, respectively) found significantly decreased CV event and myocardial infarction risks with each 6 months of anti-TNF therapy (adjusted hazard ratios 0.87 and 0.80, respectively); subgroup analyses revealed reduced CV event risks in patients aged ≥50 years and those without prior methotrexate therapy (0.86 and 0.85, respectively).

Session: Long-term outcomes of modern treatment; Oral presentation 0002

http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0002

Are patient global and fatigue predictive of structural outcomes, 3 years later, in patients in remission in early arthritis? Results from the French ESPOIR cohort

Authors: Gossec L et al

Summary: This analysis of 776 ESPOIR study participants with early arthritis followed for 3 years found moderate agreement between ACR/EULAR remission (7.4% at 6 and 12 months) and near and fatigue remission (18.7% and 3.1%, respectively; κ values 0.51 and 0.39). Prediction of radiographic remission was strongest in models with near and ACR-EULAR remission.

Session: Long-term outcomes of modern treatment; Oral presentation 0003

http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0003

Comment: This session examined some aspects of the long-term effects of treatment of rheumatic diseases, particularly CV outcomes. These two presentations were of particular interest.

Nurmohamed presented a study from a group led by Dan Furst that found that use of anti-TNF therapy was associated with a reduction in risk of CV events in RA patients compared with other therapies. In this study, methotrexate use was not associated with a reduction in CV risk. Modelling suggested that use of a TNF-inhibitor for 3 years would halve the risk of a CV event, although the study itself was not able to show this, given the relatively short average length of observation.

Gossec presented data that compared various definitions of remission – ACR/EULAR remission, near remission (remission on all criteria except patient global) and fatigue remission (near remission plus remission from fatigue), with erosive progression. Near remission was much more common than remission or fatigue remission and was just as predictive as full remission. The implication is that the patients who have a poor perception of their health may have as good a prognosis as those who feel well, and that definitions of treatment success that include patient global may be setting the bar unnecessarily high, at least as far as structural outcomes are concerned.

METABOLIC AND CRYSTAL DISEASES OF JOINTS AND BONE

Toll-like receptor 4 agonists MRP 8 and MRP 14 act as endogenous enhancers of MSU-crystal induced IL-1 secretion in vitro and reflect disease activity in gout patients in vivo

Authors: Holzinger D et al

Summary: These researchers found that MRP8 and MRP14 were released by monosodium urate-activated human neutrophils and monocytes, and they induced pro-IL-1β production in monocytes. In human and murine monocytes and macrophages, MRP costimulation increased monosodium urate-induced IL-1β secretion. MRP levels found in the synovia and synovial fluid of patients with active gout were significantly higher than levels in patients with osteoarthritis, and were positively associated with disease activity.

Session: Metabolic and crystal diseases of joints and bone; Oral presentation 0099
http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0099

Gout in patients with stable coronary heart disease and the impact of serum uric acid levels on adverse cardiovascular outcomes

Authors: Rothenbacher D et al

Summary: This long-term follow-up of 1056 study participants with coronary heart disease explored the associations between serum urate levels, inflammatory cytokines and atherosclerosis. Participants with gout at baseline (n=229) had higher C-reactive protein, IL-6 and serum urate levels. The incidence of subsequent fatal/nonfatal CV disease (21.1 per 1000 patient-years) was significantly positively associated with serum urate (adjusted hazard ratio 2.8 for highest versus lowest level quartile), but not C-reactive protein.

Session: Metabolic and crystal diseases of joints and bone; Oral presentation 0100
http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0100

Presence of tophi and high level hyperuricemia are associated with increased risk of mortality in patients with gout

Authors: Perez-Ruiz F et al

Summary: The impact of gout severity variables on mortality was prospectively investigated in 706 patients with gout in this observational cohort study. Variables significantly associated with increased mortality risk included the presence of subcutaneous tophi (adjusted hazard ratio 1.99) and the two highest quartiles of baseline serum urate level (2.44 and 2.93, respectively); death was CV-related in most cases.

Session: Metabolic and crystal diseases of joints and bone; Oral presentation 0102
http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0102

Hypouricemia due to high urate renal excretion in septic systemic inflammatory response syndrome

Authors: Pardo V et al

Summary: These researchers explored the presence and significance of changes in serum urate levels related to alterations in urate renal handling in 17 consecutive patients with severe sepsis or septic shock. An inverse correlation was seen between serum urate level and fractional excretion of urate, with presence of shock associated with lower serum levels and higher excretion. There was also a notable correlation between increased renal fractional excretion of urate and higher APACHE II scores.

Session: Metabolic and crystal diseases of joints and bone; Oral presentation 0104
http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0104

Effect of BCX4208 add-on therapy to allopurinol 300mg on plasma hypoxanthine and xanthine concentrations in gout patients

Authors: Bantia S et al

Summary: Patients with gout and a serum urate level ≥6.0 mg/dL (n=278) were randomised to receive oral BCX4208 5 mg/day (n=39) 10 mg/day (38), 20 mg/day (41) or 40 mg/day (36) or placebo (40) for 12 weeks with continued allopurinol 300 mg/day. Compared with placebo, BCX4208 was associated with significant dose-dependent decreases in plasma xanthine and hypoxanthine levels, confirming the mechanism of action of the agent.

Session: Metabolic and crystal diseases of joints and bone; Oral presentation 0106
http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0106

Comment: This session was a particular highlight at EULAR. As has become usual at this meeting, the session was in an obscure and remote room that was too small for the numbers attending, suggesting that organisers have still not caught up with the current high level of interest in gout.

Holzinger's paper demonstrated that Toll-like receptor-4-mediated secretion of MRP8 and MRP14 were capable of stimulating IL-1β secretion in monosodium urate crystal-stimulated neutrophils and macrophages. In serum and synovial fluid from gout patients, levels of MRP8 and MRP14 correlated with disease activity.

Rothenbacher presented work that correlated serum uric acid levels with risk of subsequent CV events in patients with stable CV disease, regardless of a diagnosis of gout. Compared with the lower quartile, patients in the other quartiles for serum urate had significant increases in risk, even within the normal range.

Perez-Ruiz showed that standardised mortality rates were significantly increased in patients with high levels of hyperuricaemia and in patients with tophaceous gout. He suggested that treatment of gout before it becomes severe is required, and that treatment of higher levels of hyperuricaemia may be justified, even before the development of gout in some cases.

Pardo gave an elegant demonstration of reduction in serum urate levels caused by increases in fractional excretion of urate in the presence of nongouty systemic inflammation (septicaemia). This strongly suggests that gout-related reductions in serum urate are caused by this mechanism, rather than gout being precipitated by hypouricaemia as has been suggested, or even less plausibly, that precipitating crystals take urate out of circulation, as is sometimes proposed.

Bantia presented data from a clinical trial of a new urate-lowering therapy; a drug that inhibits purine nucleoside phosphorylase upstream of xanthine and hypoxanthine. Patients had hyperuricaemia despite allopurinol 300mg daily. Data for serum urate and acute gout were not presented, but the drug reduced levels of xanthine and hypoxanthine in a dose-dependent manner.

TREATMENT STRATEGY IN RA

COBRA-light therapy is clinically non-inferior to original COBRA therapy in the treatment of early rheumatoid arthritis

Authors: den Uyl D et al

Summary: This noninferiority trial randomised patients with early, active RA to methotrexate and prednisone at respective dosages of 7.5 mg/week and 60 mg/day tapered to 7.5 mg/day with sulfasalazine 2 g/day (COBRA therapy; n=81) or 25 mg/week and 30mg tapered to 7.5 mg/day (COBRA-light therapy; n=83). Preliminary 6-month results showed that COBRA-light was noninferior to COBRA, with the difference in the changes in DAS44 score (–2.50 and –2.18, respectively) being smaller than the clinically relevant difference (p=0.08). Minimal disease activity was achieved by 49% and 41% of COBRA and COBRA-light recipients, respectively.

Session: Treatment strategy in RA; Oral presentation 0151
http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0151

Impact of comorbidities on both disease activity and treatment strategy in patients with rheumatoid arthritis: analysis of the IORRA cohort database

Authors: Nakajima A et al

Summary: This prospective analysis of the 5317 IORRA study participants identified 975 (18.3%) with ≥1 comorbidity. Moreover, higher Charlson Comorbidity Index scores were associated with higher disease activity measures and less intensive treatment strategies (i.e. methotrexate, biologicals). The authors concluded that management of patients with RA and comorbidities *"is a major issue in the biologic era"*.

Session: Treatment strategy in RA; Oral presentation 0152
http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0152

Clinical and radiological outcomes of four disease activity driven treatment strategies

Authors: van den Broek M et al

Summary: The BEST study randomised patients with recent-onset RA to sequential monotherapy, step-up combination therapy, initial combination with prednisone or initial combination with infliximab; the treatments were DAS score ≤2.4 targeted. Findings of the 347 participants still in follow-up at 8 years included: i) persistently very low radiological damage; ii) maintenance of functional ability (which had improved initially, albeit earlier with initial combination therapy than with initial monotherapy); and iii) stabilisation of clinical and drug-free remission rates.

Session: Treatment strategy in RA; Oral presentation 0154

http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0154

Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in early rheumatoid arthritis: 2-year quality of life results of the randomised, controlled SWEFOT trial

Authors: Karlsson JA et al

Summary: Participants with RA from the SWEFOT trial with DAS28 score >3.2 after 3–4 months of methotrexate monotherapy were randomised to receive add-on infliximab (n=128) or sulfasalazine plus hydroxychloroquine (n=130). There were no significant between-group differences in UK EQ-5D utility and accumulated quality-adjusted life-year gains over 21 months of follow-up, although dropout in the sulfasalazine/hydroxychloroquine arm was significantly greater than in the infliximab arm.

Session: Treatment strategy in RA; Oral presentation 0155

http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0155

Inhibition of structural damage with two intensive treatment strategies using infliximab or high dose intravenous steroid followed by treat to target in DMARD naïve rheumatoid arthritis (the IDEA study) – a preliminary report

Authors: Nam JL et al

Summary: Patients with early, DMARD-naïve RA were randomised to receive infliximab 3mg/kg on weeks 0, 2, 6, 14 and 22 then dose adjusted from week 26 according to DAS44 (n=55), or IV methylprednisolone 250mg at week 0, with placebo infusions for blinding on weeks 2, 6, 14 and 22, and (unblinded) treatment escalation (see abstract) from week 26 if DAS >2.4 (n=57); all participants received methotrexate 10 mg/week increased to 20mg by week 6, and other biologicals were allowed from week 26. Both the initial treatments, together with tight disease control, prevented radiographic progression in most participants, and no between-group differences were seen at any evaluation timepoint (26, 52 and 78 weeks).

Session: Treatment strategy in RA; Oral presentation 0156

http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0156

Comment: The COBRA study was one of the first to show that early intensive treatment of RA gave long-term advantages over the step-up approach. Den Uyl presented a comparison of the original COBRA regimen with a modified version that increased the starting dose of methotrexate from 7.5mg to 25mg, removed sulfasalazine and halved the dose of prednisone to 30mg. 'COBRA-light' is perhaps closer to usual practice, and it is therefore of interest that there were no clinically significant differences between the two regimens.

Nakajima presented a study in Japanese RA patients that showed that comorbidity was associated with higher disease activity and a tendency to use lower doses of methotrexate in response to this. It is widely recognised that comorbidities can lead to the use of more modest treatment targets – this concept is included in the treat-to-target recommendations.

Van den Broek presented data from the BEST study out to 8 years of follow-up, at which time there was very little difference between the four groups. Significantly more subjects in the group treated with infliximab from the outset were still on the initial step than those in the other groups. HAQ scores were significantly better in the infliximab group than in the step-up combination therapy group. There were no longer any differences in radiological progression. These data suggest that patients who respond to oral DMARDs can do just as well in the long term as patients treated with biological therapy, as long as they are treated to target.

This concept was further supported by the data from the SWEFOT study presented by Karlsson, in which quality of life in methotrexate-inadequate responders randomised to the addition of infliximab was not superior to those treated with the addition of sulfasalazine and hydroxychloroquine.

Nam presented the IDEA study from Emery and colleagues in Leeds. In essence, patients were randomised to receive IV methylprednisolone 250mg or infliximab at identical intervals. DAS28 remission was achieved more frequently in the infliximab group, although the difference was not significant, and there was no significant difference in erosive progression over 18 months. Once again it seems that outcome is dependent on the level of remission, regardless of how that is achieved.

PERSONALISED MEDICINE

Identification of serological biomarker profiles associated with early response to tocilizumab in rheumatoid arthritis

Authors: Bay-Jensen AC et al

Summary: This analysis of data from tocilizumab recipients with RA in the LITHE study revealed significantly greater decreases in baseline levels of biomarkers of cartilage degradation (C2M) and synovial inflammation (C3M) in tocilizumab responders (n=102) than in nonresponders (n=33). Traditional bone biomarkers and C-reactive protein levels did not differ significantly between tocilizumab responders and nonresponders.

Session: Personalised medicine; Oral presentation 0127

http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0127

Metabolic profiling of urine samples predicts response to anti-TNF therapy in patients with rheumatoid arthritis

Authors: Kapoor SR et al

Summary: These researchers identified differences in baseline urine metabolic profiles from 19 patients with RA between those who responded well to infliximab or etanercept and those who did not. Sensitivity and specificity of several urinary metabolites for predicting response to anti-TNF agents according to EULAR criteria were 85.9% and 85.7%, respectively; metabolites that predicted a response were erythritol, phenylacetic acid, p-cresol, propionic acid, methylamine, citrate, hippuric acid and creatinine. Similar urinary metabolites were seen in 20 patients with psoriatic arthritis who responded to anti-TNF therapy, but their ability to predict response could not be evaluated.

Session: Personalised medicine; Oral presentation 0128

http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0128

Comment: In spite of the revolutionary effect of TNF inhibitors in the treatment of inflammatory arthritides, 30–40% of patients do not respond to these agents. The ability to predict which patients will respond to which therapies could save time and money. Bay-Jensen presented a study of patients in the phase 3 LITHE tocilizumab trial that showed that reductions in markers of cartilage and synovial turnover predicted early response to tocilizumab better than C-reactive protein and markers of bone turnover. It remains to be seen how this could be used in practice, but it is an interesting mechanistic observation.

Kapoor showed that certain baseline urinary metabolites (e.g. citrate, creatinine, cresol) predicted response to TNF inhibitors with a sensitivity and specificity of around 85%. These studies raise the prospect of designing treatment strategies for individuals on the basis of specific patient and disease characteristics.

RA PROGNOSIS, PREDICTORS, OUTCOMES

Successful control of disease activity and treatment with biologics increase the life expectancy in rheumatoid arthritis patients

Author: Listing J et al

Summary: This analysis of German registry data of 8613 patients with RA (mean disease duration and observation time 10.3 and 3.4 years, respectively) found that while compared with the general population, RA patients had a standardised mortality ratio of 1.6 [95% CI 1.4, 1.8], effective treatment that results in persistent disease control increased life expectancy. Compared with nonbiological DMARDs, TNF inhibitor use was associated with reduced mortality risk (adjusted hazard ratio 0.65 [p=0.0004]), while rituximab and other biologicals were associated with similar risks (0.81 [p=0.34] and 0.84 [p=0.42], respectively).

Session: RA prognosis, predictors, outcomes; Oral presentation 0047

http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0047

Orthopaedic interventions for RA have changed over the period 1986–2011. An evaluation of joint surgery rates and DMARD/anti-TNF treatment patterns in two UK inception cohorts

Author: Nikiphorou E et al, and Early Rheumatoid Arthritis Study (ERAS), Early Rheumatoid Arthritis Network (ERAN)

Summary: Orthopaedic surgery rates were compared between the Early RA Study (ERAS) and the Early RA Network (ERAN) cohorts, representing the periods 1986–1999 and 2002 onwards, respectively. The overall orthopaedic surgery rates decreased from 38% in ERAS to 17.5% in ERAN, due mainly to declines in intermediate type surgeries of the wrist, hands and feet from 8 to 6 per 1000 patients per year, and not total joint replacements.

Session: RA prognosis, predictors, outcomes; Oral presentation 0048

http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0048

Comment: Listing and colleagues' data showed that mortality in RA was linked to disease activity. Use of corticosteroids was associated with an increase in mortality of 20% per 5mg of prednisone. Biological therapies were associated with an apparent decrease in mortality, but the authors took a more conservative approach in concluding that biologicals did not increase mortality. These data are reassuring, and add to the evidence that RA treatments do not increase the risk of death.

Nikiphorou presented a study that showed a decline in the rate of orthopaedic interventions between 1986 and 2011, particularly hand and foot operations. This coincided with an increase in the use of methotrexate as first-line therapy and a decrease in the interval from diagnosis to DMARD use from 3 months to 2 weeks. Hip and knee surgery rates did not change, suggesting a different mechanism or that improvements in RA treatments were more protective for small joints than for large.

HEAD-TO-HEAD BIOLOGICAL STUDIES

Abatacept SC versus adalimumab on background methotrexate in RA: one year results from the AMPLE study

Authors: Schiff M et al

Summary: The 24-month, phase 2b AMPLE study randomised biological-naïve patients with active RA inadequately responsive to methotrexate to receive SC abatacept 125mg each week (n=318) or SC adalimumab 40mg biweekly (n=328), with continued stable-dose methotrexate. The 12-month ACR20, -50 and -70 rates, kinetics of response, inhibition of radiographic progression and adverse event rates were similar between the abatacept and adalimumab arms, while abatacept was associated with fewer discontinuations and injection-site reactions.

Session: Update on non-anti-TNF biologics; Oral presentation 0022

http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_OP0022

Tocilizumab (TCZ) monotherapy is superior to adalimumab (ADA) monotherapy in reducing disease activity in patients with rheumatoid arthritis (RA): 24-week data from the phase 4 ADACTA trial

Authors: Gabay C et al

Summary: Methotrexate-unsuitable or -intolerant patients with RA for ≥6 months were randomised to receive IV tocilizumab 8 mg/kg every 4 weeks (n=163) or SC adalimumab 40mg every 2 weeks (n=162), both with appropriate placebo injections for blinding, for 24 weeks. Compared with adalimumab, tocilizumab was associated with superior improvements in signs and symptoms of RA, including the primary endpoint of change in baseline DAS28 at 24 weeks (–3.3 vs. –1.8; p<0.0001). Adverse events were similar between the groups and were consistent with previously reported data.

Session: Late breaking abstract 0003

http://www.abstracts2view.com/eular/view.php?nu=EULAR12L_LB0003

Comment: Abatacept is a biological therapy that inhibits T-cell activation in response to antigen presentation. It's effectiveness as a treatment for RA has been demonstrated in previous trials but its role in the management of RA has not been fully established. The AMPLE study may not achieve this goal, but it does at least provide evidence that abatacept is not inferior to adalimumab after one year of treatment.

Although clinical trials of TNF and B-cell inhibitors have shown that these agents are little more effective than methotrexate when given as monotherapy, they are used in this way in approximately one third of patients. In previous clinical trials, tocilizumab has been found to be superior to methotrexate when studied head-to-head as monotherapy. The ADACTA study compared adalimumab and tocilizumab, each as monotherapy in a phase 4 study over 24 weeks. Response as measured by changes in DAS28 scores, frequency of DAS28 remission and low disease activity and ACR20/50/70 scores were significantly greater in the tocilizumab monotherapy group than in the adalimumab group. Cost-effectiveness data would be helpful in determining whether methotrexate-intolerant RA patients should be treated with tocilizumab in preference to other biologicals.