Making Education Easy
11-14 June 2014, Paris, France

In this review:

Abbreviations used in this review:

ACR = American College of Rheumatology;
CDS = Colour-Doppler sonography; **CRP** = C-reactive protein;
CTA = computerised tomography angiography;
DAS = Disease Activity Score;
DMARDs = disease-modifying antirheumatic drugs;
HAQ = Health Assessment Questionnaire;
MRA = magnetic resonance angiography; **OR** = odds ratio;
PBS = Pharmaceutical Benefits Scheme;
PET = positron emission tomography; **PRP** = platelet-rich plasma;
PsA = psoriatic arthritis; **RA** = rheumatoid arthritis;
RCT = randomised controlled trial; **TNF** = tumour necrosis factor

Welcome to this review of EULAR 2014. The aim of the European League Against Rheumatism (EULAR) is to provide a forum of the highest standard for basic and clinical scientific, educational and social exchanges among rheumatology professionals, along with liaising with patient organisations to advance the clinical care of patients with rheumatic diseases.

This review has been created to allow those unable to attend, but with a keen professional interest, to access a summary of some of the presentations. Selection and review of the research has been carried out independently by Associate Professor Les Barnsley, who attended EULAR 2014.

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

Kind Regards,

Dr Janette Tenne

Medical Research Advisor

janette.tenne@researchreview.com.au

Treatment of epicondylitis by ultrasound-guided local injections of autologous conditioned plasma (ACP®): a double-blind placebo-controlled randomized clinical trial with 1-year follow-up

Authors: Le Goux P et al.

Summary: This double-blind, randomised, placebo controlled trial in 50 patients (34 men, mean age 47 years) with epicondylitis, tested the efficacy of two local injections of growth factors-containing platelet-rich plasma (PRP) under ultrasound guidance. No significant difference in mean relative pain improvement (visual analog scale; primary endpoint) was observed between PRP and placebo recipients after 6 months (-63.2% vs -69.7%; p = 0.24). Pain score decreased from 6.8 at baseline to 2.5 at 6 months and 1.65 at 12 months in PRP recipients and from 7 to 2.1 and 1.8 in control recipients. Across both groups 34% of all patients were asymptomatic at 6 months and 66% were asymptomatic at 1 year. At 1 year, 23.8% across both groups reported persistent pain.

Comment: Injections of platelet-rich plasma are widely used in practice in Australia. This study casts doubt upon the efficacy of this treatment. Although small, it was well designed and appropriately powered for the primary endpoint. There was no difference between the injections of normal saline and platelet-rich plasma in terms of pain relief. Both groups did quite well and this raised questions as to whether the injections of saline had more than a placebo effect, equating to "prolotherapy". My own thoughts were that the researchers were simply documenting the natural history of the disease under clinical trial conditions.

Presentation: OP0013
http://www.abstracts2view.com/eular/view.php?nu=EULAR14L_OP0013&terms=

Pathogenic mechanisms in giant-cell arteritis

Author: Cid MC

Summary: Several genetic polymorphisms have been associated with increased susceptibility to giant cell arteritis with the strongest association being with major histocompatibility complex class II variants, suggesting it may be an antigen-driven disease, although no triggering antigen has been identified. Activated dendritic cells in lesions are thought to play an important role in T-cell activation, and giant cell arteritis exhibits marked T-helper (Th) 1-mediated immune response with strong expression of interferon (IFN)-γ and IFNγ-induced molecules. Th17 immune response also plays a role and patients with marked interleukin (IL)-17 expression show better glucocorticoid response. IFNγ potently activates macrophages that release the pro-inflammatory cytokines IL-1, TNF-α and IL-6 and the expression in tissue of TNF-α and IL-6, and increased serum concentrations of these cytokines are associated with persistent or relapsing disease. Both chemokines and adhesion molecules expressed in lesions amplify inflammatory loops, while angiogenic factors increase neovascularisation and allow infiltration of leukocytes. These processes amplify and maintain inflammatory lesions. Meanwhile activated macrophages generate reactive oxygen species that induce oxidative damage and vessel wall injury. In addition, matrix metalloproteases (MMP-9 and MMP-2) are present in lesions, contributing to elastic fibre disruption and abnormal vascular remodelling. Giant-cell arteritis treatment is based on symptomatic improvement through the use of glucocorticoids, but sustained remission occurs in only 30-40% of patients. TNF blockade with various agents has not maintained remission, presumably due to cytokine pathway redundancy. Multicentre clinical trials of tocilizumab blockade of IL-6 receptors or abatacept interference with CD28-mediated T-cell co-stimulation are being conducted. The multifunctional cytokine IL-6 induces the acute phase response and related symptoms, but in addition maintains activation of the Th17 pathway. Activated macrophages and injured vascular smooth muscle cells release growth factors that induce myofibroblast differentiation, migration and matrix protein production leading to intimal hyperplasia and vessel occlusion. Myofibroblast activation may also be stimulated by platelet-derived growth factors, transforming growth factor β and endothelin-1, which are not down-regulated by glucocorticoids, suggesting a specific approach may be required for the treatment of vessel occlusion.

Comment: See page 3, "The old and the new in the treatment of giant cell arteritis".

Presentation: SP0002
http://tinyurl.com/qz7qke3

The role of imaging modalities in the diagnosis and followup of giant cell arteritis

Author: Pipitone N.

Summary: Colour-Doppler sonography (CDS), magnetic resonance angiography (MRA) and contrast-enhanced computerised tomography angiography (CTA) are useful in diagnosing early arteritis before vascular complications such as stenoses and aneurysms develop, by visualising inflammation in temporal and large arteries, which are not easily accessible to biopsy, including both the arterial wall and the lumen. Inflammatory signs include vessel wall thickening and transmural oedema, observable as a hypoechoic "halo" around an inflamed artery lumen on CDS and as contrast enhancement on MRA and CTA. CDS is useful for assessing superficial arteries, while CT and MR is useful for deep, large vessels such as the thoracic and abdominal aorta. Large-vessel inflammation can also be assessed by 18F-fluorodeoxyglucose positron emission tomography (PET); however it can't show changes in temporal or renal arteries nor is it able to show anatomical details of the arterial wall, and cannot detect stenoses or aneurysms. CDS, MRI/MRA, and CT/CTA can detect both arterial wall and lumen changes, while PET can also monitor vascular inflammation in large vessels. Digital subtraction angiography may have a role in guided intervention.

Comment: See page 3, "The old and the new in the treatment of giant cell arteritis".

Presentation: SP0003
http://tinyurl.com/p4ug4s7

EULAR 2014 Conference Review™

Independent commentary by Associate Professor Les Barnsley.

Les holds Medicine, Epidemiology and Philosophy degrees. He is a Fellow of the Royal Australasian College of Physicians and a Scientific Fellow of the Faculty of Rehabilitation, Royal Australasian College of Physicians. He is Senior Staff Specialist and Head in the Department of Rheumatology at Concord Hospital and Associate Professor in the Department of Medicine at the University of Sydney.

Associate Professor Barnsley has contributed chapters to textbooks and has over 50 articles in peer-reviewed journals, including two in the *New England Journal of Medicine.* He was a member of the Expert Writing Committee for the 1st and 2nd editions of *Therapeutic Guidelines in Rheumatology.* He has been the Principal Investigator in several industry-sponsored trials of therapies for RA and OA. His research interests include spinal pain, whiplash, musculoskeletal medicine,medical education and general rheumatology.

The old and the new in the treatment of giant cell arteritis

Author: Gonzalez-Gay MA

Summary: Giant cell arteritis manifests clinically as a result of arterial wall inflammation, which causes structural changes, including intimal hyperplasia and internal elastic laminae fragmentation and luminal occlusion. The most common symptom is headache, but visual ischaemic manifestations, and permanent visual loss are the most serious complications. Primary therapy with corticosteroids (prednisone 40-60 mg/day as a single or divided dose for 3-4 weeks) has reduced the frequency of blindness, and patients without severe ischaemic complications experience rapid disease improvement. In those with severe visual ischaemic complications, higher steroid doses, (prednisone 60 mg/day or methylprednisolone pulse therapy 1 g/day for 3 days) are advised. The time from onset of symptoms to the first dose of corticosteroids predicts improvement of visual loss; however, the prognosis for significant visual recovery once the disease is established is poor. Immunosuppressive agents in large vessel vasculitis may be considered as adjunctive therapy; in particular methotrexate may be of use with severe corticosteroid-related adverse events and/or with prolonged corticosteroid therapy for relapse. Meta-analysis of RCT trials in newly diagnosed patients suggested only modest efficacy of methotrexate 10-15 mg/week for reducing relapse rate and decreasing cumulative corticosteroid dosage. Anti-TNF-α therapy has had no clear benefit; however, anti-IL6 receptor monoclonal antibody therapy may be effective in patients with inflammatory aortitis refractory to other biologics and corticosteroids.

Comment: This series of lectures and abstracts considered aetiology, imaging and treatment of giant cell arteritis. Cumulative evidence points to an antigen driven disease mediated in the first instance through the innate immune system. Subsequent downstream processes involve both TH17 and TH1 responses from T lymphocytes, and there also is a role for B cells. Of particular interest was the observation that early in the course of the disease, inflammation is the key pathological abnormality, but later on vascular occlusion occurs because of proliferation of myointimal cells. This raises issues about the types of treatment that might work at different times over the course of the disease, particularly whether monoclonal antibodies directed at vascular growth factors might have a role to play. This is particularly pertinent since corticosteroids do not downregulate many of these vascular growth factors. In considering imaging, since the original observation of ultrasound demonstration of vasculitis there have been important developments in ultrasound technology that permit more accurate detection of the "halo sign", a hypoechoic region around the inflamed artery corresponding to oedema. A meta-analysis reported this sign to be 75% sensitive and 83% specific for giant cell arteritis. This is reasonable, but still means that you can't use it to rule out the condition. It was also noted that these ultrasound changes resolved rapidly with the institution of corticosteroid therapy. Given the need for an accurate diagnosis and the serious consequences of a missed diagnosis, I don't think that ultrasound should yet replace temporal artery biopsy where this is available. There were no major new controlled studies concerning treatment of giant cell arteritis. Previous trials have found no benefit from methotrexate, hydroxychloroquine or TNF-α inhibitors added to corticosteroids. The most promising reports are open studies concerning the use of tocilizumab in refractory cases.

Presentation: SP0004
http://tinyurl.com/mcq8hk9

Apremilast, an oral phosphodiesterase 4 inhibitor, is associated with long-term (52-week) improvement in measures of disease activity in patients with psoriatic arthritis: results from 3 phase 3, randomized, controlled trials

Authors: Kavanaugh A et al.

Summary: This pooled analysis of 52-week data from the randomised, controlled PALACE 1, 2 and 3 trials sought to assess the effect of apremilast 20 or 30 mg twice daily on psoriatic arthritis. More apremilast than placebo recipients achieved a modified American College of Rheumatology 20% (ACR20) response at 16 weeks (primary endpoint) and this response was sustained over 52 weeks in patients initially randomised to apremilast. Apremilast also improved disease activity at week 16 as measured by the Disease Activity Score-28 (DAS28) based on C-reactive protein (DAS28-CRP), modified Psoriatic Arthritis Response Criteria (PsARC) response, and a good or moderate European League Against Rheumatism (EULAR) response. In those continuously receiving apremilast for 52 weeks, sustained improvements were observed. The most common adverse events were diarrhoea (12.2%), nausea (10.1%) and headache (8.0%).

Comment: See adjacent "Fifty-two week clinical response to brodalumab..."

Presentation: OP0078
http://tinyurl.com/kodbrqp

Ustekinumab is effective in inhibiting radiographic progression in patients with active psoriatic arthritis: integrated data analysis of two phase 3, randomized, placebo-controlled studies

Authors: McInnes I et al.

Summary: The effect of ustekinumab 45 mg or 90 mg in inhibiting structural damage in patients with active psoriatic arthritis was assessed in this pooled analysis of the randomised, placebo-controlled PSUMMIT 1 ($n = 615$) and PSUMMIT 2 ($n = 312$) trials. Both ustekinumab 45 mg and 90 mg recipients experienced a smaller change from baseline in total Psoriatic Arthritis (PsA) modified van der Heijde-Sharp (vdH-S) scores at week 24 than placebo recipients (0.39 and 0.40 vs 0.97; $p = 0.017$ and $p < 0.001$), and this inhibition continued through week 52. Patients randomised to placebo who switched to ustekinumab at weeks 16 or 24 also exhibited slowing of radiographic progression by week 52 (mean total vdH-S change 0.08). PSUMMIT 1 data demonstrated this effect when evaluated in isolation, whereas in PSUMMIT 2, a demonstrable effect was not observed, although this may be due to missing radiographic data (23% of placebo-treated patients).

Comment: See below

Presentation: OP0079
http://tinyurl.com/ktzpuss

Fifty-two week clinical response to brodalumab, an anti-IL-17R antibody, in subjects with psoriatic arthritis

Authors: Mease PJ et al.

Summary: This randomised, placebo controlled phase 2 study examined long-term effects of brodalumab, a human anti-interleukin-17 receptor A monoclonal antibody, in 168 patients (mean age 52 years; mean disease duration 8.7 years). Of 159 patients who completed the 12 week evaluations, 22 discontinued by week 52. ACR20 and ACR50 response rates were higher in brodalumab 140 and 280 mg every two weeks (Q2W) than placebo recipients at week 12 (40% and 44% vs 19%) and continued to improve during an open-label extension (all participants receiving brodalumab 280 mg Q2W) through week 52 (71%, 56% and 50%). Adverse events reported by ≥5 patients in any treatment group through week 52 were nasopharyngitis, arthralgia, psoriatic arthropathy, upper respiratory tract infection, bronchitis, nausea, sinusitis and oropharyngeal pain. Ten patients reported serious adverse events including acute myocardial infarction, invasive ductal breast carcinoma, metastatic lung cancer, melanoma, pyelonephritis and streptococcal septic arthritis. No neutropaenia adverse events were reported although there were eight neutropaenia cases of ≤grade 2 based on laboratory values. No deaths or mycobacterial/fungal/opportunistic infections occurred.

Comment: The two main areas of therapeutic progress for psoriatic arthritis discussed this year were the small molecule apremilast, a twice-daily oral phosphodiesterase inhibitor (PDE4), and drugs acting on the IL-12/23 IL-17 pathway, of which ustekinumab is the most progressed. The PDE4 inhibitors work through intracellular regulation of inflammatory mediators. Data on three studies (PALACE 1, 2 and 3) were presented in a single talk, and overall showed benefits over a 1-year treatment course. The main adverse events noted in patients on apremilast were diarrhoea and nausea. Although it is not yet clear exactly where this agent will fit into the treatment matrix for psoriatic arthritis (the outcomes were based on ACR20 responses) it is encouraging to see a new option for those patients unable to take TNF inhibitors or other agents such as methotrexate. The ustekinumab studies PSUMMIT 1 and PSUMMIT 2 have demonstrated the clinical efficacy of the drug in patients who are biologic naïve and who have been exposed to TNF-α inhibitors respectively. Further data were presented by the inimitable Professor Iain McInnes concerning the effect on radiographic progression. This was an a priori designed, pooled analysis of the two studies to achieve sufficient power. Overall there was inhibition of radiographic progression in the active treatment arm. The effect was less marked in the group in which prior TNF-α inhibitors had been permitted. It was not clear whether this was due to a specific effect of having been on the TNF-α inhibitors or a spurious result arising from a conservative analysis of missing data. It also became apparent in the ensuing discussion that assessing radiographic progression in this disease is more complex than in rheumatoid arthritis, principally because of the slow progression of x-ray changes in psoriatic arthritis. Also, it is clear that the skin responds particularly well to ustekinumab. The anti IL-17 drug brodalumab, acting downstream from ustekinumab, also showed some promise for both skin and joints, and further confirms the importance of the IL-17 pathway in psoriatic skin disease, arthritis, and probably other spondyloarthropathies.

Presentation: SAT0404
http://tinyurl.com/lq3r5fh

No increased risk of congenital malformations after preconception paternal exposure to DMARDs

Authors: Wallenius M et al.

Summary: This analysis of data from the Medical Birth Registry of Norway 2000-11 examined the occurrence of congenital malformations in offspring of 3866 males with inflammatory joint diseases exposed to disease-modifying antirheumatic drugs (DMARDs) ≤3 months prior to conception (n = 110). Overall the incidence of congenital malformations was not associated with exposure to DMARDs (4/110 [3.6%] vs 17869/596711 [3%]).

Comment: I am slightly envious of the Scandinavians. Their record linkage provides excellent opportunities to answer important questions. This study used links between databases of inflammatory rheumatic diseases, the use of DMARDs and a national database of severe congenital malformations. Pre-conception paternal exposure to DMARDs was not associated with an increased risk of major congenital malformations. However, only severe malformations were considered and the confidence intervals for the point estimate were relatively wide. Nevertheless, I consider that this provides some reassurance particularly for patients whose pregnancy may not have been planned. The relatively small numbers of pertinent observations, despite an entire Scandinavian country as the sampling frame, highlights the difficulty of establishing a definitive answer to these questions, and means we must continue to tolerate a degree of ambiguity.

Presentation: OP0199
http://tinyurl.com/lb5x553

Induction of clinical remission followed by drug-free withdrawal with abatacept combination and monotherapy in early RA: results from the AVERT study over 18 months

Authors: Emery P et al.

Summary: This phase IIIb, randomised controlled study examined the effect of subcutaneous abatacept in 351 patients with early rheumatoid arthritis. After 12 months, 60.9%, 42.5% and 45.2% of patients receiving abatacept plus methotrexate (n = 119), abatacept (n = 116) or methotrexate (n = 116) achieved a DAS28 (CRP) score of <2.6. The OR for abatacept plus methotrexate versus methotrexate was 2.01 (95% CI 1.18-3.43; p = 0.01), that for abatacept versus methotrexate was 0.92 (95% CI 0.55-1.57). Efficacy based on DAS28 (CRP) in the abatacept monotherapy arm generally fell between the abatacept plus methotrexate and methotrexate arms. After treatment withdrawal at 12 months, most patients discontinued as a result of increased disease activity (177/223; 79.4%). Only 14.8%, 12.4% and 7.8% of patients receiving abatacept plus methotrexate, abatacept, and methotrexate, respectively, maintained DAS28 (CRP) <2.6 at both 12 and 18 months. In a post hoc analysis, those who maintained DAS28 (CRP) <2.6 at both 12 and 18 months tended to have numerically lower baseline mean symptom duration, DAS28 (CRP), HAQ score and DAS28 (CRP) <2.6 over time during treatment compared with those who achieved only DAS28 (CRP) <2.6 at 12 months. Over 12 months of treatment, serious adverse events occurred in 6.7%, 12.1% and 7.8% of abatacept plus methotrexate, abatacept and methotrexate recipients, respectively; serious infections occurred in 1, 4 and 0 patients.

Comment: This study is interesting for a number of reasons. Firstly, reflecting the new paradigms of rheumatoid arthritis management, the endpoint is remission rather than a degree of improvement. The groups were all anti-citrullinated antibody positive, and had active disease, so would be expected to do poorly. They were also methotrexate and biological naïve. The combination of abatacept and methotrexate achieved impressive rates of DAS improvement and even strict Boolean remission. This occurred in an increasing proportion of patients over the first twelve months, greatest in the combination group of abatacept and methotrexate. The drugs were stopped after 12 months, and depending on the remission criteria selected, between 10 and 20% from the combination group remained in remission 6 months later with less in the single drug arms. From an Australian perspective, we can't use abatacept in this fashion under the PBS guidelines, but it does highlight the possibility that we can induce lasting drug free remission in a small but useful proportion of our patients. It also makes me feel a little more comfortable in withdrawing therapy in patients who are keen to see how they go off biological treatment.

Presentation: OP0026
http://www.abstracts2view.com/eular/view.php?nu=EULAR14L_OP0026&terms=

Conference Reviews are prepared with an independent commentary from relevant specialists. To become a reviewer please email geoff@researchreview.com.au

Research Review is an independent medical publishing organisation producing electronic journals in several specialist areas. These journals provide summaries of the 'must see' studies from the most respected medical journals in the world together with a local specialist commentary indicating why they matter. **Privacy Policy:** Research Review will record your email details on a secure database and will not release them to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time.

Disclaimer: This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

RESEARCH REVIEW™ the Australian perspective

