

Meeting report

## **Ninth Asia Pacific League Of Associations For Rheumatology (APLAR) Congress, Beijing, China, 21–26 May, 2000**

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### **Abstract**

The Congress covered the broad field of rheumatology, with participants from China, the Asia Pacific League of Associations for Rheumatology (APLAR) region and the rest of the world. The programme consisted of a mix of plenary lectures, concurrent symposia, workshops, free paper sessions and poster presentations. Basic sciences were well represented, with the general theme of inflammatory cytokines being of particular interest. One plenary lecture and a number of other presentations addressed the problem of atherosclerosis and rheumatic diseases. Diseases prominent in the region, such as Behcet's disease and Takayasu's disease, were represented with large series. Other areas of interest were musculoskeletal infections in HIV-positive patients and the management of spondyloarthritis. Although the use of the most recently developed drugs is restricted in the APLAR region because of cost factors, there were symposia on the latest pharmacological advances such as COX-2 technology, leflunomide and anti-tumour necrosis factor (TNF) therapy.

**Keywords:** atherosclerosis, Behcets, congress, cytokines, summary

### **Introduction**

The Ninth Asia Pacific League of Associations for Rheumatology (APLAR) Congress was held in conjunction with the Chinese Rheumatology Association Congress of Rheumatology in Beijing, China, from May 21–26, 2000. The meeting was jointly organised by the Chinese Rheumatology Association and the Chinese Medical Association. There were approximately 2000 registrants, with 400 from China and others from the APLAR region and other Leagues.

The meeting consisted of 20 plenary lectures, 39 concurrent symposia, 17 workshops, six free paper sessions and four poster sessions. Altogether there were 263 oral and

468 poster presentations. The broad area of rheumatology was covered during the meeting; this report will concentrate on some highlights of the Congress.

### **Review**

#### **Inflammatory cytokines**

M Bendele *et al* (University of Colorado and Amgen Inc., USA) described the effects of interleukin 1 receptor antagonist (IL-1Ra, in a hyaluronic acid slow-release vehicle), pegylated soluble TNF receptor I (sTNF-RI) and both used simultaneously in several animal models of arthritis. IL-1Ra and pegylated sTNF-RI are the recombinant human forms of naturally occurring inhibitors of these

APLAR = Asia Pacific League of Associations for Rheumatology; AS = ankylosing spondylitis; CRP = C-reactive protein ESR = erythrocyte sedimentation rate; IL-1Ra = interleukin 1 receptor antagonist; IVDU = intravenous drug user; NOD = non-obese diabetic; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; ODF = osteoclast differentiation factor; PBMC = peripheral blood mononuclear cells; PCP = pulse cyclophosphamide; RA = rheumatoid arthritis; SSc = systemic sclerosis; sTNF-RI = pegylated soluble tumour necrosis factor receptor I; TNF = tumour necrosis factor.

cytokines. There was increased benefit from the combination, providing a preclinical rationale for investigating the potential for combination therapy with these cytokine inhibitors in early phase clinical trials.

Li Yigong (Fuzhou General Hospital, China) and Shi Guiying (PLA General Hospital, Beijing, China) investigated Th1 and Th2 subsets at the sites of rheumatoid inflammation, and also the expression of IL-18 in rheumatoid arthritis (RA) joints at both mRNA and protein levels, in an attempt to understand the relationships between the expression of IL-18 and the ratio of Th1 to Th2 cells, and between IL-18 levels and disease activity. They found that levels of IL-18, IL-4 and IFN- $\gamma$  mRNA were higher in peripheral blood mononuclear cells (PBMCs) and synovial tissue in RA patients than in osteoarthritis (OA) patients and controls. Positive immunohistochemical staining for IL-18 antibody was found in all RA synovial tissues, but infrequently in OA synovium, and was absent in controls. *In situ* hybridisation with an IL-18 probe showed similar results. A positive correlation was seen between IL-18 mRNA levels and IFN- $\gamma$  mRNA from synovial and PBMC samples in RA, and also between IL-18 mRNA levels and disease activity (as assessed by erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP] levels). They concluded that IL-18 may be involved in stimulating the IFN- $\gamma$ -dominated Th1 responses in inflammatory sites in rheumatoid arthritis and may be related to disease activity.

William Arend *et al* (University of Colorado, USA) examined the roles of the secreted isoform of IL-1Ra (sIL-1Ra) and of the intracellular isoform (icIL-1Ra) in human and murine cultured cells and in murine collagen-induced arthritis. They concluded that IL-1Ra exerts anti-inflammatory effects outside cells by blocking IL-1R binding and inside cells by inhibiting phosphorylation of key signal transduction pathways.

The results of a study on the effect of treatment with pegylated recombinant human soluble tumor necrosis factor-type 1 receptor (PEG sTNF-R1) on the progression of diabetes and sialadenitis in the non-obese diabetic (NOD) mouse model (with mice aged 8-25 weeks) were presented by R Fox *et al* (Scripps Medical and Research Foundation, USA). Treatment blocked the development of autoimmunity (both diabetes and sialadenitis) in contrast to findings in previous reports showing increased cases of diabetes when adult NOD mice were treated with anti-TNF antibodies. TNF may play a role in Sjögren's syndrome and type 1 diabetes.

#### Mononuclear cells and formation of osteoclasts

The role of TNF- $\alpha$  and IL-1 $\alpha$  on synovial macrophage-osteoclast differentiation was reported by Y Fujikawa *et al* (Oita Medical University, Japan). Their studies showed

that TNF induces RA synovial macrophage-osteoclast differentiation and that IL-1 $\alpha$  activates osteoclasts to resorb bone. Osteoclast formation and activation was independent of the osteoclast differentiation factor (ODF) signalling system. Bone resorption in response to IL-1 $\alpha$ /TNF may have an important role in RA joint destruction.

I Itonaga *et al* (Oita Medical University, Japan) had previously shown that osteoclastic bone-resorbing cells were derived *in vitro* from macrophages isolated from arthroplasty specimens. Their current study investigates whether macrophages that have phagocytosed particles are capable of differentiating into osteoclastic bone-resorbing cells. Particle-phagocytic macrophages in the pseudomembrane surrounding the implant (latex particles) not only produced cytokines, but also differentiated into osteoclasts. This may influence bone resorption and lead to loosening of a prosthesis.

#### Atherosclerosis and rheumatic diseases

Yehuda Schoenfeld (Tel Aviv University, Israel) discussed the role of autoimmunity in atherosclerosis in a plenary lecture. His group has previously shown that immunisation of low-density lipoprotein (LDL)-receptor-deficient mice with  $\beta$ 2 glycoprotein-1 ( $\beta$ 2GP1), a principal target of 'auto-immune' antiphospholipid antibodies, enhances early atherosclerosis. He reported studies showing direct evidence for a role of antigen ( $\beta$ 2GP1)-reactive T cells in promoting atherosclerotic lesions in these mice.

JK Alkaabi *et al* (Ninewells Hospital and Medical School, Dundee, Scotland) presented data on the prevalence of macrovascular disease in RA. RA patients had an increased prevalence of lower limb arterial disease. The prevalence of smoking, diastolic blood pressure levels and glucose levels were similar in the RA and control groups. The intima-media thickness, as assessed by carotid duplex scans, suggested this was atherosclerotic in nature. Systolic blood pressure was significantly higher in the RA patients (138 versus 125 mmHg) and 60% of the RA patients had been on steroids for more than 3 months, possibly contributing to the higher rate of ischaemic heart disease in this group of patients.

YB Park *et al* (Yonsei University College, Korea) studied the effect of anti-inflammatory treatment on lipid profiles before and after treatment in 42 RA patients not previously treated with steroids or disease-modifying antirheumatic drugs. They showed that HDL-cholesterol and apolipoprotein A1 (apoA1) levels were significantly higher and the ratio of apoB/apoA1 significantly lower after treatment. Patients with active, uncontrolled RA had altered lipid profiles which might expose them to a higher risk of atherosclerosis. The suppression of inflammation in RA not only helped control the arthritis, but also lowered the risk of cardiovascular disease.

Meilien Ho *et al* (Ninewells Hospital and Medical School, Dundee, Scotland) have previously reported an increased prevalence of macrovascular disease in systemic sclerosis (SSc). Basic atherosclerotic risk factor profiling had not shown a cause for this. In this study, they investigated whether elevated homocysteine and oxidised LDL (OxLDL) levels might be involved. SSc patients had a trend to higher homocysteine levels, possibly caused by malabsorption of folate. OxLDL levels were higher in diffuse SSc, reflecting increased oxidative stress. These findings may contribute to the increased severity of vascular disease in SSc patients.

### **Spondyloarthritis**

Muhammad Khan (Metro-Health Medical Centre, Cleveland, USA) discussed the treatment of ankylosing spondylitis (AS). Patient education enhances compliance with drug therapy and a regular lifelong exercise programme. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be used at their full anti-inflammatory doses. Studies of COX-2-specific NSAIDs are under way. Concurrent use of more than one NSAID provides little extra benefit but increased toxicity. Sulphasalazine may be helpful for peripheral arthritis, but has little effect on axial arthritis or enthesitis. Oral steroids are of no value in the long-term management of musculoskeletal aspects of AS but local steroids for recalcitrant peripheral joint synovitis, enthesitis or sacroiliitis can provide short-term relief. Peripheral synovitis may respond to methotrexate. Studies of other agents, such as thalidomide and pamidronate, are under way. Preliminary studies suggest that anti-TNF therapy may hold great promise in severe AS unresponsive to conventional therapy, with a rapid clinical improvement and a dramatic fall in acute phase reactants occurring in an open study.

F Huang and J Gu (PLA General Hospital, Beijing, China) reported an open study of five patients with refractory AS treated with thalidomide. Four responded, with only minor adverse effects. Z Ye *et al* (Shenzhen People's Hospital, China) reported a study in AS comparing thalidomide ( $n=29$ ) with sulphasalazine ( $n=37$ ) and with NSAIDs alone ( $n=32$ ). Thalidomide and sulphasalazine were more effective than the NSAID group, with no major differences between these two agents. Adverse effects were more common with thalidomide, but they were not serious.

GC Liang and WG Barr (Northwest Medical School, Chicago, USA) presented an open study of leflunomide in 12 patients with recalcitrant psoriatic arthritis. Eight had moderate to marked improvement in both psoriasis and arthritis.

### **Musculoskeletal infections in patients with HIV infection**

W Louthrenoo (Chang Mai University, Thailand) reviewed musculoskeletal infections in patients with HIV infection.

These are not uncommon in northern Thailand, where HIV infection is endemic. *Staphylococcus aureus* is the most common organism in bone and joint infection in HIV-positive intravenous drug users (IVDUs). Non-IVDUs usually had non-typhoidal salmonella, streptococci or other Gram-negative bacteria. Although acute monoarthritis and oligoarthritis are common presentations, polyarthritis is also seen. The arthritis usually involves large joints. Fungal bone and joint infections are not uncommon, usually due to *Penicillium marneffe*, a dimorphic fungus endemic in north Thailand and southern China.

### **Behcet's Disease**

F Davatchi (Tehran University, Iran) presented a comparative study of eight treatment methods for ocular manifestations in 1056 patients with Behcet's disease. The treatments used in this open, nonrandomised study were pulse cyclophosphamide (PCP), low dose PCP, oral cyclophosphamide, weekly methotrexate, chlorambucil, cyclosporine A, azathioprine, and combined low-dose PCP and methotrexate. Patients had active posterior uveitis and/or retinal vasculitis. The majority of patients in each group improved, with no significant differences between groups.

F Khosravi and S Samangoeei (Nemazi Hospital, Shiraz, Iran) reported findings in 15 Behcet's patients from south-west Iran who had central nervous system involvement (out of a total cohort of 500 Behcet's patients). Nine presented with a thrombotic cerebrovascular accident, one with a cerebral artery aneurysm, three with raised intracranial pressure, one with facial and neck swelling, one with tonic/clonic convulsion and one with aseptic meningitis. Central venous sinus thrombosis was subsequently detected in four patients. Thirteen were male and two female. The mean age was 27.4 years (11–45). The mean interval between onset of disease and CNS involvement was 9 years; the mean follow up was 4.5 years (8 months to 12 years). Five patients had CNS involvement as the first disease manifestation. At final follow up, twelve patients were fully functional, two had degrees of gait abnormalities and one remained bedridden. This is interesting because of the regional bias and the large series studied.

### **Takayasu's arteritis**

S Jain *et al* (Postgraduate Institute of Medical Education and Research, Chandigarh, India) presented the clinical profile of 124 patients with Takayasu's arteritis seen from 1979–1999 at a tertiary care hospital. The diagnosis was established on aortography or autopsy. There were 77 females and 47 males. The mean age was  $27.8 \pm 9.1$  years. Hypertension was the most common mode of presentation (76%), with Takayasu's arteritis being the commonest cause of secondary hypertension in India. This is interesting because of the regional bias and the large series studied.

## **Conclusion**

The Congress consisted of a well balanced mix of review sessions and presentations of basic and clinical research. There was strong regional representation as well as involvement from participants and speakers from other areas worldwide.

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