RHEUMATOLOGY SYMPOSIUM

19 September 2003

SESSION 1

ADVANCES IN UNDERSTANDING RHEUMATOID ARTHRITIS

Chairman: Dr RA Luqmani, Consultant Rheumatologist, Western General Hospital, Edinburgh

HOW EARLY SHOULD WE DIAGNOSE 'EARLY ARTHRITIS'?

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ABSTRACT

Background: It is increasingly apparent that significant, and often irreversible, damage occurs within the first year of clinically apparent disease in rheumatoid arthritis (RA).[1,2] This suggests a need for the early diagnosis of persistent inflammatory arthritis and the early introduction of appropriate treatment.[3] A number of studies on RA have assessed the effect of aggressive therapy instituted within the first two to three years of disease.[4,5] When compared with more conservative therapies, these approaches slow the rate of progression of structural damage. They do not, however, switch the disease off. A fundamental question remains as to whether there is an early 'therapeutic window' in patients with inflammatory arthritis destined to persistence, before the pathological substrate that defines persistent disease is established, and during which therapy may switch off the inflammatory response permanently.

Rheumatoid synovitis is characterised by an expansion of the fibroblast network and an inhibition of lymphocyte apoptosis (mediated by fibroblast derived interferon beta (IFN-β)), phenomena central to the persistence of inflammation.[6–8] In established RA, the accumulating lymphocytes stimulate macrophage tumour necrosis factor alpha (TNF-α) production through contact-dependent mechanisms. We have proposed that an expansion of the fibroblast network, and an inhibition of lymphocyte apoptosis, define the switch to persistence, and that before this occurs, patients who would otherwise develop persistence are within a therapeutic window. This hypothesis was supported by the observation that in gout there is no inhibition of lymphocyte apoptosis, and the disease resolves rapidly and spontaneously.[7]

Methods: Patients with very early synovitis (<12 weeks duration) were recruited through an early inflammatory arthritis clinic. High resolution ultrasound was used to guide aspiration/lavage from small joints of the hands, wrists and ankles in patients with early disease.[9] Synovial fluid lymphocyte apoptosis was assessed, and T-cell-related cytokines were measured using a multiplex microbead system.

Results: In the majority of patients with very early inflammatory arthritis, whose disease progressed to persistence, lymphocyte apoptosis was inhibited from initial presentation. In a minority of patients, however, apoptosis was detectable at initial presentation, within a few weeks of symptom onset, though it was found to be inhibited in follow-up samples obtained after 12 weeks. By contrast, there was significantly more lymphocyte apoptosis in synovial fluid samples of patients with self-limiting inflammatory arthritis. Intriguingly, in 40% of patients with self-limiting synovitis, lymphocyte apoptosis was inhibited at presentation, during the early inflammatory response. In many of these patients, however, lymphocyte apoptosis was apparent on a subsequent joint aspiration, during the resolution phase of the response. This pattern is similar to that seen during the resolution of the cutaneous delayed-type hypersensitivity (DTH) response,[10] and suggests that an inhibition of lymphocyte apoptosis in the early stages of disease may not be the result of a fixed expansion of the fibroblast network, but may be operating through more transient mechanisms.

Analysis of synovial fluid cytokines demonstrated the presence of interleukin-2 (IL-2), IFN-γ, IL-12, IL-4 and IL-10 in a sub-group of patients with disease destined to persistence within the first 12 weeks but not in patients with persistent synovitis after 12 weeks or in those with self-limiting disease.

Conclusions: An assessment of lymphocyte apoptosis and T-cell related cytokines suggests that there is a group of patients with inflammatory arthritis destined to persistence, in which unique pathological mechanisms

are operating within the first three months of disease. Therapeutic interventions during this window may have qualitatively superior effects compared with the later introduction of treatment. Many regard 'early arthritis' as arthritis within the first year of disease – early disease that is truly different from longstanding disease may be significantly earlier than this.

Speaker profile: No details supplied

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KEY WORDS

Early arthritis, therapeutic window, apoptosis, cytokines, ultrasound

SPONSORS

Arthritis Research Campaign (ARC)

DECLARATION: None

WHAT IS THE ROLE OF FIBROBLASTS IN RHEUMATOID ARTHRITIS?

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ABSTRACT

Background: One of the most important questions in arthritis research is not why inflammation occurs in joints but why it persists. Current models of inflammation stress the role of antigen-specific lymphocyte responses and attempt to address the causative agent. Recent studies, however, have begun to challenge the primacy of the lymphocyte and have begun to focus on an extended immune system in which stromal cells, such as macrophages and fibroblasts play a role in the persistence of the inflammatory lesion.

Methods: Not submitted

Results: We have found that stromal cells such as fibroblasts are important in regulating the switch from acute resolving to chronic persistent inflammation associated with the pathology of diseases such as rheumatoid arthritis. Fibroblasts from the rheumatoid synovium provide survival and retention signals for lymphocytes leading to inappropriate and persistent accumulation of leucocytes within inflamed tissue. Furthermore synovial fibroblasts directly influence the endothelial 'post code' and endothelial cell function allowing enhanced and inappropriate leucocyte recruitment.

Conclusions: Our work suggests that targeting the stromal microenvironment is likely to be an important strategy for future anti-inflammatory therapies.

Speaker profile: I obtained my first degree (BA) in Biochemistry from the University of Oxford (1985) with subsequent undergraduate training in Medicine MBBS at the Royal Free Hospital, London (1990). Postgraduate Medical training MRCP (1993) in General Medicine at Hammersmith Hospital, London (Mark Walport, Dorian Haskard), and John Radcliffe Hospital, Oxford. DPhil (1996) arising from Wellcome Training Fellowship with Professor J Bell and Dr D Simmons at the Institute of Molecular Medicine, Oxford. In 1996, funded by a Wellcome Clinician Scientist Fellowship, I joined the Department of Rheumatology in Birmingham. In October 2000 I was appointed Senior Lecturer in the

Division of Immunity and Infection, Birmingham. In October 2001, I was awarded an MRC Senior Clinical Fellowship and in October 2002 became ARC Professor of Rheumatology, Division of Immunity and Infection, MRC Centre for Immune Regulation in Birmingham (http://rheuma.bham.ac.uk/NewSite/department/site.htm).

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KEY WORDS

Fibroblasts, chemokines, cell adhesion, cytokines, rheumatoid arthritis, leucocytes

SPONSORS

Arthritis Research Campaign, Medical Research Council

DECLARATION

I receive funding from Celltech, from whom I also receive consultancy fees.

SESSION 2

DIFFICULT MANAGEMENT PROBLEMS IN RHEUMATOLOGY

Chairman: Professor R Sturrock, McLeod/ARC Professor of Rheumatology, Centre for Rheumatic Diseases, Glasgow

WHAT LESSONS CAN WE LEARN FROM THE STUDY OF PAIN PATHWAYS IN RHEUMATIC DISEASE?

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ABSTRACT

Background: Inflammatory mediators contribute to pain either by directly activating nociceptor (pain) fibres or more commonly by sensitising these fibres to mechanical and other stimuli. Nociceptor activation leads to the sensation of pain and also the peripheral release of peptides that may, in turn, modify the subsequent course of the inflammatory response. This presentation addresses the critical interaction between inflammation and the sensory nervous system.

Methods: Not submitted

Results: Nociceptor sensitisation involves early post-translational changes to receptors/ion channels and later, longer-lasting transcription-dependent phenotypic switching. As an example of this latter phenomenon, we have shown that whereas articular nociceptors have relatively low-level expression of tumour necrosis factor receptor (TNF-R) expression under normal conditions, inflammation increases both TNF-R messenger ribonucleic acid (mRNA) and protein expression, thereby helping to explain the analgesic efficacy of anti-TNF therapy in rheumatic disease.

Neurogenic inflammation is mediated, at least in part, by the sensory neuropeptides, substance P (SP) and neurokinin A (NKA). We have assessed the contribution of SP to the pathogenesis of arthritis using mice with a disruption of the SP receptor, neurokinin-1 receptor (NK-1). Neurokinin-1 receptor knock-out mice showed significantly less footpad swelling and mechanical hyperalgesia than wild-type animals in an Freund's complete adjuvant (FCA) arthritis model. Histological and radiological scores were markedly reduced in the knock-out group. The differential effect was particularly marked with respect to scores for synovial hyperplasia and inflammatory cell infiltrate. Consistent with this, leukocyte migration across endothelial cell layers was substantially reduced by a mechanism involving the chemokine monocyte chemoattractant protein 1 (MCP-1). Cell rolling and adhesion are unaffected. Furthermore SP substantially modified cellular responses to other mediators including interleukin-1 (IL-1) and TNF.

Conclusions: The immune system acts in concert with the nervous system to constitute an interactive, communicative network. Ongoing studies are revealing the considerable overlap with respect to mediators and underlying cellular and molecular mechanisms. It is apparent that so-called 'anti-inflammatory' drugs have important analgesic actions within the nociceptive system whereas 'analgesic' drugs may act to influence the process and outcome of persistent inflammatory disease.

Speaker profile: No details supplied

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KEY WORDS
Pain, inflammation, cytokines, growth factors, neuropeptides.

SPONSORS
No details supplied

DECLARATION
No details supplied

IS SECONDARY AMYLOIDOSIS A TREATABLE DISEASE?

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ABSTRACT

Background: Reactive systemic (AA, secondary) amyloidosis occurs in 1–5% of patients with chronic inflammatory rheumatic diseases.[1] It usually presents with nephropathy and is progressive and often fatal within five to ten years. AA amyloid fibrils are derived from the circulating acute phase reactant serum amyloid A protein (SAA). The development of serum amyloid P (SAP) scintigraphy, a quantitative method for imaging amyloid deposits, and assays for measuring SAA concentration have provided new insights into the natural history and management of patients with AA amyloidosis.[2,3]

Methods: We have used a combination of SAP scintigraphy and frequent measurements of SAA to study the relationship between fibril precursor protein production, amyloid load and clinical outcome among more than 300 patients with AA amyloidosis whose underlying inflammatory diseases were treated as vigorously as possible. Experimental therapies including cytokine blocking agents were evaluated in some cases.

Results: Amyloid deposits regressed in 60% of patients whose median SAA values were sustained within the reference range (<10 mg/L), and amyloidotic organ function stabilised or improved in 90% of these cases. Outcome varied substantially between patients whose median SAA concentration exceeded 10 mg/L, but amyloid load increased and organ function deteriorated in most patients whose SAA remained above 50 mg/L. Estimated survival at ten years was 90% in patients whose median SAA was under 10 mg/L, and 40% among those whose median SAA exceeded this value ($p<0{\cdot}0009$).[4] Treatment that succeeded in adequately reducing SAA production included chlorambucil, anti-tumour necrosis factor (TNF) and anakinra.[5]

Conclusions: Although amyloid fibrils are unusually stable, AA amyloid deposits are turned over *in vivo*, and outcome is favourable in AA amyloidosis when the SAA concentration is maintained below 10 mg/L. Treatment strategies in patients with AA amyloidosis should be guided by frequent serial estimations of serum SAA concentration, and the latter provides invaluable prognostic information. Therapy that reduces SAA production to within the reference range prevents further accumulation of AA amyloid deposits, frequently leads to amyloid regression and improvement in amyloid-related organ dysfunction, and significantly improves long-term survival. The efficacy of experimental drugs that might have a direct effect on the amyloid deposits remains under investigation.

Speaker profile: Not submitted

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KEY WORDS
AA amyloidosis, SAP scintigraphy, serum amyloid A protein

SPONSORS
Medical Research Council

DECLARATION
No conflicts of interest were involved in these studies.

SIR JAMES CAMERON LECTURE

Chairman: Dr NDC Finlayson, President, Royal College of Physicians of Edinburgh

TARGETED THERAPY IN VASCULITIS

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ABSTRACT

Background: Strategies for the modulation of cytokines in vasculitis have enormous potential to improve treatment for patients, but rigorous studies are required to determine their true efficacy and optimal uses. In recent years, efforts have focused on strategies of tumour necrosis factor (TNF) inhibition, with studies ranging from preliminary investigations to multi-centre, randomised, double-masked trials. Other targeted approaches of interest include B-cell depletion with rituximab, and strategies designed to inhibit B-lymphocyte stimulator (BLyS). With the nearly complete status of some randomised clinical trials in Wegener's granulomatosis (WG) and the plans for the rapid accomplishment of trials in other diseases (e.g. giant cell arteritis), we are poised to gather solid evidence about the role of these approaches.

Methods: Not applicable

Results: The principal approach to targeted therapy in vasculitis to date has centred around an anti-cytokine strategy, particularly anti-TNF. Open-label studies performed with both etanercept (a fusion protein) and infliximab (a chimeric monoclonal antibody) suggest that larger trials of these agents are indicated. Randomised trials of etanercept in WG are now in advanced stages of performance, and a randomised trial of infliximab in giant cell arteritis will begin soon. Data with regard to efficacy in Crohn's disease and differing toxicity profiles suggest that important differences may exist with regard to the efficacy of anti-TNF approaches in vasculitis.

B-cell depletion with the use of rituximab (a chimeric anti-CD20 monoclonal antibody) is a potentially paradigm-shifting approach to the treatment of anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV). To date, 11 patients with severe refractory AAV have been treated with rituximab in a compassionate use protocol. Following rituximab, circulating B-cells became undetectable and ANCA-titres decreased significantly. Remission was achieved in all and maintained while B-cells were absent. A randomised, multi-centre trial of rituximab in AAV is now in the protocol development phase.

An alternative approach to B-cell inhibition may be through the modulation of BLys (also known as BAFF, TALL-1, zTNF4, THANK and TNFSF13B), which plays a critical role in maintaining B-cell homeostasis. Excessive BLys signalling may lead to B-cell-mediated immunopathology. Recent studies have confirmed the presence of elevated levels of BLys in WG. Strategies designed to inhibit BLys are likely to be tested in the next few years.

Conclusions: The results of ongoing trials of targeted therapies will answer many questions about the roles of these agents and are almost certain to raise others. As the field of vasculitis investigation moves forward, the following points must be borne in mind:

- Treatment approaches that are effective in one type of disease will not always translate to another.
- All forms of TNF inhibition are not alike. The same is undoubtedly true for other forms of target therapy as well.
- Finally, treatments that are effective in some patients with one disease may not be equally effective in all patients with the same disorder. Our ability to predict patients' responses based on dose, genotype, clinical phenotype and other variables remains rudimentary, and will be an area of further investigation for many years to come

Speaker profile: Not supplied

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KEY WORDS
Vasculitis, Wegener's granulomatosis, TNF, rituximab, BLys

SPONSORS
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DECLARATION
No details supplied

SESSION 3

FUTURE TREATMENT OF RHEUMATOID ARTHRITIS

Chairman: Professor C Pitzalis, Professor of Experimental Rheumatology, GKT School of Medicine, London

ARE THERE ANY NEW TREATMENTS FOR RHEUMATOID ARTHRITIS?

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ABSTRACT

Background: New therapies for rheumatoid arthritis (RA) are increasingly 'biological' – genetically engineered proteins. Many are designed to have anti-inflammatory effects through cytokine blockade, as for anti-tumour necrosis factor (TNF) agents. New targets include interleukin-6 (IL-6) and IL-15. Other agents are designed to suppress or deplete specific cell populations. The major new cellular target in RA is the B lymphocyte. B-lymphocyte depletion therapy with rituximab was first used in 1998. A high level of efficacy has been shown in a phase-II controlled trial. This presentation will focus on experience at University College London (UCL) with repeated usage over a period of up to five years.

Methods: Thirty-seven patients have been recruited to a programme of repeated B-cell depletion therapy for RA. Protocols have been based on rituximab, combined with cyclophosphamide in early cases. Sixty-two treatments have been given over 4·5 years. Patients are withdrawn for (i) poor response (American College of Rheumatology 20 (ACR20)); (ii) successful re-introduction of disease modifying anti-rheumatic drugs (DMARDs); (iii) toxicity.

Results: Twenty-five patients continue on the programme with evidence of response and a further three patients have regained control on re-introduction of DMARD (methotrexate, sulphasalazine). All four immunoglobin M (IgM) rheumatoid-factor-negative patients failed to respond. One seropositive patient achieved no benefit and two benefits of five months or less. Two have been lost to follow-up. The mean period of benefit (>ACR20) was 15 months with a maximum of 35 months. One patient showed inadequate depletion. Secondary failure of clinical response or depletion was not observed in up to four repeat treatments. Co-existent psoriasis on three patients showed no change. B-cell depletion protocols were well-tolerated. Eight febrile episodes with pulmonary symptoms have occurred in 85 patient years of follow-up. All settled on antibiotic. One suspected joint prosthesis infection was sterile on culture. Three patients who received rituximab in combination with cyclophosphamide have developed breast carcinoma (2) or carcinoma *in situ* (1) although in one case there was evidence that this pre-dated therapy. (No increase in incidence of carcinoma has been reported in surveillance of rituximab usage elsewhere.) In three cases where patients have received three courses of therapy in rapid succession, serum IgM levels have fallen to undetectable during the period of depletion. Falls in IgG levels have been modest and antibacterial antibody levels well-maintained.

Conclusions: Experience with repeated B-cell depletion therapy in RA suggests that approximately 80% of seropositive patients may become susceptible to continuing control of disease, but seronegative disease appears unresponsive. Secondary resistance appears not to be a problem over two to four years. Susceptibility to chest infection may be increased. Cumulative effects on immunoglobulin levels may occur with frequently repeated usage.

Speaker profile: No details supplied

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KEY WORDS
Rheumatoid arthritis, B lymphocyte depletion, rituximab

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DECLARATION
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MATRIX METALLOPROTEINASES IN RHEUMATOID AND OSTEOARTHRITIS

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ABSTRACT
Background: The breakdown of cartilage collagen in both rheumatoid arthritis (RA) and osteoarthritis (OA) causes irreversible damage. The extracellular matrix of cartilage, which contains collagen, aggrecan and minor components, is maintained by the chondrocytes. Imbalance between the synthesis and degradation of this matrix leads to long-term joint damage.

The matrix metalloproteinases (MMPs) are a family of potent enzymes that can degrade extracellular matrix and that are upregulated by proinflammatory cytokines. Mixtures of cytokines can potently upregulate individual MMPs that, once activated, can destroy cartilage collagen.

Methods: We have used a combination of an *in vitro* cartilage model, cell culture and routine biochemical analyses and enzyme assay.

Results: Combinations of interleukin-1 (IL-1) and oncostatin M (OSM) promote cartilage collagen breakdown *in vivo*.[1] Chondrocytes in culture produce markedly raised levels of MMPs in response to this combination. Different signalling pathways are unregulated by this combination of cytokines and provide the potential for new therapeutic interventions.[2] Animal models show that these cytokines cause severe joint destruction.[3] Protection of the cartilage can be seen with tissue inhibitor metalloproteinases (TIMPs), low-molecular-weight MMP inhibitors, serine proteinase inhibitors and the growth factors transforming growth factor ß (TGF ß) and insulin-like growth factor 1 (IGF1).[4]

Conclusions: Cartilage collagen breakdown occurs in both RA and OA, and although the initiating factors are different the final common pathway involves active MMPs.

Speaker profile: Not submitted

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KEY WORDS
chondrocyte, cartilage, interleukin-1, oncostatin M, collagen, RA, OA

SPONSORS
ARC, Nuffield Foundation, FARNE

DECLARATION
None

SHOULD ALL PATIENTS WITH INFLAMMATORY RHEUMATIC DISEASES BE TAKING STATINS?

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ABSTRACT
Background: Rheumatoid arthritis (RA) is associated with increased mortality and reduced life expectancy, which for severe RA are comparable to those of triple vessel coronary heart disease or some lymphomas. The commonest single cause of death in RA is cardiovascular disease (CVD). This accounts for up to 55% of all deaths in RA, and is increased with standardised mortality ratios ranging between 1·13 and 5·25 in multiple studies. The reasons for this remain unclear, but most investigators believe that it is due to accelerated atherosclerosis leading to premature development of ischaemic heart disease (IHD), acute coronary

syndromes (ACS) and death.[1]

Methods: We and others have performed a series of studies trying to characterise in RA: (i) the prevalence and nature of cardiovascular comorbidity; (ii) the prevalence and causes of stable IHD; (iii) the outcome – and its predictors – of ACS; and (iv) the potential role of inflammatory processes in the generation of early IHD in RA.[1]

Results: Collectively, cardiovascular (CV) comorbidity is highly prevalent in RA. One-third of unselected hospital RA patients have known CV comorbidity but, more alarmingly, more than half of the remaining two-thirds also have either significant CV risk factors or previously undetected CVD. Rheumatoid arthritis patients display many features of the dysmetabolic syndrome, including hypertension, dyslipidaemia, altered body composition and prothrombotic factors. Definite evidence of cardiac ischaemia can be detected in 50% of unselected RA patients using stress myocardial perfusion imaging, and although in most cases this appears to be due to classical atherosclerotic coronary artery disease, in others it appears to be due to smaller-vessel, steroid-responsive, probably vasculitic involvement. Low-density lipoprotein (LDL) activation and macrophage activation through inflammatory pathways may be of pathogenic importance.

Conclusions: A number of large studies have confirmed the beneficial role of statins in patients with established IHD as well as those at risk of developing it.[2] Many RA patients require statin therapy on the basis of classical cardiac risk assessment only. However, the RA population appears to be a high-risk group (probably due to the inflammatory load), with a risk similar to that of patients with Type 2 diabetes. The approach to statin therapy may therefore need to be different. In addition, more recent work *in vitro*, in animal models and in therapeutic outcome studies suggests that statins are pleiotropic, displaying anti-inflammatory, antithrombotic, bone-remodelling, cell-adhesion and NO-modulating effects.[3,4] This would make them good candidates for treatment of RA *per se*. I will be discussing the potential beneficial role of statins in the therapy of RA, from both the cardiac and arthritic perspective. At present, there are no published, long-term human trials in RA to confirm or refute such effects.

Speaker profile: Not supplied

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KEY WORDS

Rheumatoid arthritis, ischaemic heart disease, inflammation, statins, prevention, treatment

SPONSORS

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DECLARATION

There are no conflicts of interest.

EDITORIAL NOTE

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