EDITORIALS

GLUCOCORTICOSTEROIDS IN RHEUMATOID ARTHRITIS: LESSONS FOR THE FUTURE

While used in the treatment of rheumatoid arthritis (RA) for over 40 yr, the controversy over the appropriate use of corticosteroids remains. What scientific data exist, either pro or con, provide fuel for heated discussions. In spite of concerns for long-term safety and limited data on disease modification, a recent international multicentre study found that ~50% of all patients with RA treated by rheumatologists, whether in an academic or private practice setting, are on low-dose (<10 mg/day) prednisone [1]. In fact, at a recent consensus conference, it was concluded that low-dose steroids in addition to methotrexate should be the foundation for combination therapy in aggressive RA [2]. Therefore, from a practical standpoint, while corticosteroids are a mainstay of therapy, the scientific data supporting their use are limited.

In addition to baseline therapy in patients with severe disease, corticosteroids are used during flares and as a bridge during changes in disease-modifying anti-rheumatic drug (DMARD) therapy. In general, this means that when patients are not doing well, corticosteroid therapy is initiated and, in many situations, continued for extended periods. The major change in the use of corticosteroids appears to be the dosage, with most rheumatologists recognizing the deleterious effects of chronic 'high' doses. However, the definition of high- vs low-dose corticosteroids continues to be a major area of discussion. Even in the article by Jansen et al. [3], low doses are described as both less than 15 mg/day and 10 mg/day. The article by Hickling et al. [4] supports 7.5 mg/day as disease modifying and the work by Boers et al. [5] supports these findings. This is a critical issue as other studies suggest that doses <7.5 mg/day are not as efficacious. However, most rheumatologists have patients who are very stable on <5 mg/day in combination with a DMARD. It is common practical knowledge that patients with RA note flares with changes of as little as 1 mg/day. Long-term studies evaluating dose, especially in combination with a DMARD, are needed.

While RA is a disease that affects 1% of nearly all populations, worldwide and associated with a specific HLA class II epitope, it is a heterogeneous disease both in its course and response to anti-rheumatic therapy. Present theories suggest that affected patients are exposed to the arthritogenic agent months, and potentially years, in advance of clinical presentation. Therefore, even at the time of clinical diagnosis, RA is already a multicellular process involving lymphocytes, macrophages, endothelial cells and synovial fibroblasts, to name a few. In addition, we know that there are hormonal issues including gender specificity and the HPA axis. Unfortunately, it is impossible to define where a patient or even an individual joint is in this process or how best to proceed with therapy. The treatment of RA still remains a method of trial and error with the rheumatologist constantly working to provide the best clinical response in each patient. Even with recent biological and combination therapies, efficacy only approaches 50–70% in 60% of patients [6, 7]. True drug-free remissions occur in <10% of patients with seropositive disease. Corticosteroids provide an important intervention, especially when used in addition to other agents. Alone, the dosage needed is too high to be safe and patients ultimately become steroid dependent. However, in combination with a DMARD, a lower dose can be used for longer periods of time. The study reported here, as well as others, support this [4, 5].

Rheumatologists have known for a long time that corticosteroids are effective and have tried hard to use them safely. The studies reported here suggest that we are doing better. However, given the course of RA and the present mixtures of agents used, it is highly unlikely that a 'perfect' study will ever be performed to prove the effects of corticosteroids. It is likely, however, that they will kindle many studies and continue to provide excellent discussions for a long time.

There may be a lot to learn by looking at the various mechanisms of action of corticosteroids and the outcomes of the studies reviewed by Jansen. While rheumatologists are excited about the new agents destined to be released in the next few years, including the tumour necrosis factor (TNF) antagonists, the interleukin-1 antagonists and the COX-2-selective agents, corticosteroids provide all of these activities and then some. A single pulse of methylprednisolone is very effective at inhibiting TNF down to the level of synovial expression. Indeed, like reported TNF antagonist responses, corticosteroid therapy results in a more consistent clinical response when used in combination with DMARDs. When used long term, it appears that they have disease-modifying properties. Given the reported costs of some of these newer agents, one must question whether they will truly add anything to the therapy of RA. The lessons from corticosteroid therapy support the need for long-term studies of these newer agents, especially addressing safety and disease modification.

The long-term use of high-dose corticosteroids leads to a variety of significant side-effects, most of which we have all seen in the clinics. Most of these occur at doses >10 mg/day and rarely at doses <5 mg/day. While serious infections are a major issue, they are far less frequent at the lower doses. Similarly, osteoporosis is less at lower doses. Recent data support the use of
agents such as the bisphosphonates when using corticosteroids in younger individuals [8]. The report by Hickling et al. [4] suggests that the use of 7.5 mg/day of corticosteroids is not a problem and not associated with long-term problems.

In conclusion, the discussion on the efficacy and safety of corticosteroids only mirrors similar issues when other anti-rheumatic therapies are thoroughly reviewed. It is interesting to note that while fewer and fewer rheumatologists are using gold and D-penicillamine, they continue to use corticosteroids in most of their patients with severe RA. Their efficacy appears even better when used in combination with DMARDs. The major issue for this editor is not whether they work, but how I can best use them as safely as possible. Clinical use has already shown that they are efficacious and now they appear to be disease modifying.

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REFERENCES

FROM CRITICISM TO CREATIVITY: THE GENESIS OF THE ARC/BSR CLINICAL TRIALS GROUP

Many of us suffer the pressures of working in isolation, and regularly contemplate the nature of the evidence which drives our clinical practice. The bench-mark for evaluation of management strategies in clinical medicine is the randomized controlled trial, and ideas for such trials regularly arise during busy clinical practice. However, the translation from these ideas to the design, execution, analysis and publication of the finished product is a difficult task, and one where the busy clinician is limited by lack of time, resources, and a supporting infrastructure—a view eloquently expressed by Professor Ian Haslock in a letter to the British Journal of Rheumatology [1].

This cri de cœur initiated a series of debates within the Research Subcommittee and Scientific Co-ordinating Committee of the Arthritis Research Campaign, leading to the formation of an ARC Think Tank on clinical trials. This group took advice from many sources, including members of the Medical Research Council who have considerable expertise in multiccentred randomized trials and now an accepted base for much of haematological and oncological practice.

In recognition of the difficulties encountered by the clinical rheumatologists in the UK, a combined response from the ARC and BSR led to the evolution of a structure of support incorporating the skills of relevant professional bodies to promote clinical research on a multicentre basis, with a national direction. The ultimate objective is to enable the clinicians throughout the UK to network together and participate in clinical trials relevant to the spectrum of rheumatic diseases both common and rare. The product of these deliberations was the ARC/BSR Clinical Trials Group, which has now been ‘pump-primed’ with a £1.5 million budget from the ARC.

We believe that the current membership of the group incorporates the appropriate expertise, including clinical trials methodology, health services research and rheumatology, in order to set up and oversee the venture.

All members of the BSR will shortly receive a letter outlining the purpose of the group and how it will facilitate multicentre trials. A request will be made for members to define two key questions which need to be addressed in rheumatological practice and to provide an outline proposal giving brief details of the objectives, methodology and background. Proposals received will be prioritized using a Delphi approach (the postal request for questions followed by an analysis of the complete response after anonymization), followed by a nominal group process involving the ARC/BSR Clinical Trials Committee in which an explicit ranking of proposals will be undertaken. It is envisaged that 2–3 programmes will be supported during 1999. When the programmes have been identified, the group will
provide active support facilitating the integration of investigators and defining key investigators who will drive each proposal. The BSR in particular will assist specialist registrars in training who would be eager to join such initiatives.

This initiative represents a major commitment by both the ARC and BSR to promote directly clinically relevant research in our speciality. We encourage you to take part in this important venture, which we believe will benefit the busy clinician and our speciality, develop a ‘research ethos’ for our trainees and promote the highest quality of care to rheumatology patients.

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Reference