

# Annals of the Rheumatic Diseases

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## Leader

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### Building towards a consensus for the use of tumour necrosis factor blocking agents

Over the past 10 to 15 years, scientific advances have ushered in a new era in the treatment of rheumatoid arthritis. The aetiopathogenesis of rheumatoid arthritis is slowly being dissected and an increased understanding of the mechanisms by which tissue damage occurs in this disease is appearing.<sup>1,2</sup> This knowledge, combined with the use of molecular technology, have begun to allow medical research to pinpoint potential targets for treatment of rheumatoid arthritis. Among such targets, you could include T cells, macrophages, synoviocytes, the interaction between antigen presenting cells and T cells, the MHC and its sub-units, and numerous cytokines (for example, IL1, IL1ra, IL10, IL12, TNF $\alpha$ , etc).

This knowledge and technology have introduced a number of potential new therapeutic agents. Earlier efforts using IL2 fusion proteins were unfortunately unsuccessful.<sup>3</sup> Various anti-CD4 monoclonal antibodies have been tried to treat rheumatoid arthritis and some may still be in development.<sup>4</sup> Likewise, early trials of IL4, IL6, IL10 and IL11 are all underway.<sup>5</sup>

TNF $\alpha$  plays a very significant part in inflammation as it promotes IL1 production and augments GM-CSF, IL6 and IL8. Furthermore, it promotes the expression of adhesion molecules, which facilitate leucocyte traffic to sites of inflammation.<sup>6</sup> Increased levels of TNF $\alpha$  were found in rheumatoid arthritis and this finding was followed by early experiments showing that anti-TNF $\alpha$  antibodies were effective in both in vitro and in animal models of rheumatoid arthritis.<sup>5-10</sup> Later, chimeric monoclonal antibodies, recombinant TNF receptor fusion proteins and fully human anti-TNF antibodies were found to be remarkably effective for the treatment of rheumatoid arthritis.<sup>10-18</sup> The clinical effectiveness of this group of drugs makes it probable that ongoing studies examining the progression of radiological damage will show that effective TNF blockade will result in slowing of radiological damage in rheumatoid arthritis.

With the marketing of the first of these TNF blocking agents in the United States for rheumatoid arthritis (etanercept) and soon for Crohn's disease (infliximab) there has been a groundswell of enthusiasm for the use of these agents. However, TNF blocking agents are very expensive and their long term consequences are not yet fully understood. Consequently, the place of TNF blocking agents in the rheumatological armamentarium is not clear.

In this context, it was appropriate that a group of rheumatologists and bioscientists get together to discuss current insights into TNF blockade and also formulate a provisional consensus statement on the use of TNF blocking agents for the treatment of rheumatoid arthritis. Approximately 80 rheumatologists and bioscientists from 22 countries were chosen from a worldwide group of people who had experience or interest in the use of TNF blocking agents for rheumatoid arthritis. Because of size limitations, not everyone who might have been appropriate for such a conference could be invited to attend. The conference was, entitled "Advances in Targeted Therapies. TNF- $\alpha$  Blockade in Clinical Practice", organised under the sole responsibility of several medical schools and supported by unrestricted educational grants from six pharmaceutical manufacturers. The latter had no part in the decisions regarding the programme, attendees or participants in this consensus conference. The proceedings of this conference are published as the supplement of the December issue of the *Annals of the Rheumatic Diseases*. This includes a consensus statement on the clinical use of TNF blocking agents that was finally formulated and approved by the participants.<sup>18</sup>

The process by which consensus was reached included initial discussion in small groups, large group discussion and repeated drafts, which permitted input from all participants. As the long term consequences and effectiveness of TNF block agents are not fully understood, it was felt that the use of these new agents should be under the supervision of those physicians experienced in the diagnosis, treatment and clinical assessment of rheumatoid arthritis.

The participants agreed that candidate patients for TNF blocking agents should have active rheumatoid arthritis despite a full and adequate trial of one or more DMARDs. In addition, given the varying aggressiveness of rheumatoid arthritis in individual patients, the effect of the patients rheumatoid arthritis on their quality of life as well as symptoms and signs engendered by the disease needed to be considered. As the TNF blocking agents presently on the market or approaching market will be very expensive and the properties of these agents are not fully known, it was felt that they should lead to significant documentable improvement in symptoms and/or laboratory parameters during 8-12 weeks of treatment when given in adequate

doses. Should this improvement not have occurred within this time period, alternative treatments should be considered.

Given the many effects of TNF on inflammation and immune function, it was generally agreed that TNF blocking agents should not be started, or should be discontinued when serious infections occurred and should only be resumed if those infections are cleared and the risk of occurrence is low.

The participants at this consensus conference agreed that there were a number of situations in which the effect of TNF blockade is unknown, consequently calling for significant caution. Such situations include patients with lymphoma, lymphoproliferative disease, and, possibly, other malignancies; chronic viral infections such as HIV, hepatitis B or C; or during pregnancy or lactation.

As rare cases of lupus-like disease have occurred in patients receiving TNF blockade, such treatment should be stopped if there is clinical evidence of a lupus-like syndrome. On the other hand, the presence of a positive anti-nuclear antibody, or anti-cardiolipin antibody, in itself, did not seem to predispose patients to a clinical syndrome and, therefore, the participants felt that the presence of these antibodies (without suggestive clinical symptoms) would not prevent the use of TNF blocking agents. Furthermore, the group was unable to find evidence regarding the safety of primary vaccinations or the use of live, attenuated vaccines during TNF blockade treatment. Thus, such vaccinations need to be done cautiously and the potential consequences of those vaccinations need to be carefully considered during TNF blockade treatment.

As a certain percentage of patients given a TNF blocking agent do not respond to that treatment and as it is anticipated that TNF blocking agents will have slightly different mechanisms of action (for example, differing affinity constants, differing pharmacokinetics), it is probable that sequential use of TNF blocking agents will be considered. The consensus group agreed that it was unlikely that cross reactivity among these agents would occur, but such cross reactivity is at least theoretically possible, and once more, emphasised the need to be sure that physicians using these treatments are experienced in the diagnosis, treatment and clinical assessment of rheumatoid arthritis so that subtle but untoward toxicity can be detected.

Undoubtedly, TNF blocking treatment will be used in other diseases where TNF appears to have a pathogenetic role. As evidence supporting the use of these agents in those diseases (for example, polyarticular juvenile arthritis or psoriatic arthropathy) is accumulated, TNF blocking treatment should be used in those populations.

The current developments are exciting for patients with rheumatoid arthritis and other rheumatic diseases and their physicians. However, any consensus statement on the

use of TNF blocking treatment will change as new data regarding both efficacy and adverse events appear. Consensus statements, based upon the best evidence available at the time, may help facilitate the optimal and appropriate use of these agents, particularly by physicians who have not obtained experience in the course of clinical trials.

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