

# Tumour necrosis factor alpha inhibitors for the treatment of adult rheumatoid arthritis

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## Summary

The management of patients with rheumatoid arthritis now focuses on both the relief of symptoms and the prevention of joint damage. When conventional therapies fail, adalimumab, etanercept and infliximab, inhibitors of the pro-inflammatory cytokine tumour necrosis factor alpha, can be considered. Evidence from randomised controlled studies suggests that many patients who do not respond to conventional therapy improve with adalimumab, etanercept or infliximab, particularly when these drugs are combined with methotrexate. Infusion and injection site reactions occur in some patients and the risks of infection are increased, particularly early in the treatment course. Long-term risks such as an increased risk of malignancy are currently being evaluated.

Key words: adalimumab, etanercept, infliximab.

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## Introduction

The last decade has seen a substantial shift in the management of rheumatoid arthritis. It has moved from symptom control with the empirical use of drugs borrowed from other specialties, to 'designer' therapies, based on the known pathogenesis of rheumatoid arthritis, which alleviate symptoms and retard joint destruction. Three examples of these new therapies are adalimumab, etanercept and infliximab. These drugs inhibit the action of a key pro-inflammatory cytokine – tumour necrosis factor alpha (TNF- $\alpha$ ).

## Cytokines in the pathogenesis of rheumatoid arthritis

Rheumatoid arthritis is a systemic inflammatory disease that results in the normally bland single cell layer of synovial fibroblasts in the joint transforming into an inflammatory maelstrom that may cause bone and cartilage destruction. The

specific cause of rheumatoid arthritis remains obscure, but it is most likely a combination of a genetic predisposition, an environmental trigger and possibly a random immunological event.

Once an inflammatory process begins, the mechanisms that perpetuate and amplify it are much better understood and seem to involve an ongoing imbalance between pro- and anti-inflammatory factors. Central to this process are cytokines, particularly TNF- $\alpha$ .

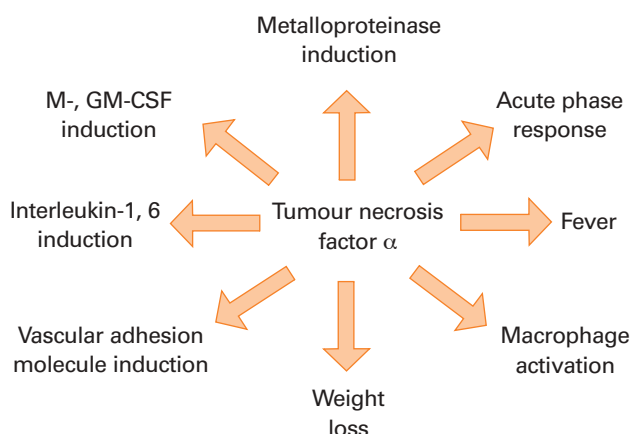
TNF- $\alpha$  is a pleiotropic pro-inflammatory cytokine with many actions that are central to the pathogenesis of rheumatoid arthritis (Fig. 1). Along with interleukin 1, another important pro-inflammatory cytokine, TNF- $\alpha$  has therefore been a target for biological therapy in rheumatoid arthritis.

## Pharmacology of TNF- $\alpha$ inhibition

TNF- $\alpha$  is predominantly produced by monocytes and activated macrophages and its activity may be potentially inhibited at a variety of sites. These include strategies that inhibit the production or release of TNF- $\alpha$  from the cell, neutralise TNF- $\alpha$  on the cell surface or in the soluble phase or block the TNF- $\alpha$  receptor or its downstream signal transduction pathway. Currently, clinical trials are examining the efficacy and toxicity of many of these strategies. Research is most advanced for strategies that neutralise TNF- $\alpha$  on the cell surface or in the soluble phase.

Fig. 1

### Actions of tumour necrosis factor $\alpha$



Infliximab was the first anti-TNF- $\alpha$  drug to be tested in rheumatoid arthritis. It is a recombinant chimeric monoclonal antibody composed of a human antibody backbone with a mouse idiotype (the region that binds TNF- $\alpha$ ). Infliximab is given by intravenous infusion.

Adalimumab is an anti-TNF- $\alpha$  monoclonal antibody that is similar to infliximab, but with a more humanised molecule. It is given by subcutaneous injection every other week.

Etanercept is also a recombinant protein composed of an immunoglobulin backbone and two p75 TNF- $\alpha$  soluble receptors. It is given as a twice-weekly subcutaneous injection.

## Efficacy of TNF- $\alpha$ inhibitors

### Symptom-modifying effects

In recent times the symptomatic outcome measures for rheumatoid arthritis trials have been standardised. Most studies have used the American College of Rheumatology (ACR) response criteria or the disease activity score (DAS).<sup>1</sup> The ACR response criteria are a composite outcome measure composed of the number of swollen and tender joints, the ESR or C-reactive protein and the patient's and physician's global assessments of the activity of the arthritis. These scores can help when comparing the different trials. Three levels are calculated for the ACR response criteria:

- ACR20 – a 20% improvement in disease measures, considered to be the minimum response perceptible by the patient

- ACR50 – a 50% improvement, considered by the patient to be a significant decrease in their arthritis severity
- ACR70 – a 70% improvement, considered to be a highly significant decrease in their arthritis severity.

### Infliximab

The efficacy and toxicity of infliximab for the treatment of patients with rheumatoid arthritis was assessed in the large multicentre Anti-Tumour necrosis factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) study.<sup>2,3</sup> This study enrolled 428 patients with rheumatoid arthritis that was active (defined as the presence of six or more swollen and tender joints, raised acute phase markers and/or early morning stiffness of more than 45 minutes) despite at least three months of oral or parenteral methotrexate at a weekly dose of at least 12.5 mg. Patients were randomised to continue their current methotrexate dose and receive either placebo intravenous infusions or one of four schedules of intravenous infliximab (3 mg/kg four or eight weekly, 10 mg/kg four or eight weekly).

The results of the ATTRACT study (Table 1) show that about 50% of the patients receiving infliximab at a dose of 3 mg/kg every eight weeks (the dose approved by the Australian Pharmaceutical Benefits Advisory Committee) achieve an ACR20 response and about 25% achieve the more clinically significant ACR50. The response is sustained over the 54 weeks of treatment.

Table 1

### Clinical outcomes from the randomised controlled studies evaluating the efficacy of tumour necrosis factor inhibitors in patients with rheumatoid arthritis

Author	TNF inhibitor (dose)	ACR20 (%)	ACR50 (%)	ACR70 (%)	Comments
Maini et al (1999) <sup>2</sup>	Infliximab (3 mg/kg 8 weekly, intravenously) with methotrexate	50	27	7	ATTRACT study results at week 30
	Methotrexate alone	20	5	0	
Lipsky et al (2000) <sup>3</sup>	Infliximab (3 mg/kg 8 weekly, intravenously) with methotrexate	42	21	10	ATTRACT study results at week 54
	Methotrexate alone	17	8	2	
Moreland et al (1999) <sup>4</sup>	Etanercept (25 mg twice weekly, subcutaneously) no methotrexate	59	40	9	Results of a placebo-controlled study at six months
	Placebo	11	5	–	
Weinblatt et al (1999) <sup>5</sup>	Etanercept (25 mg twice weekly, subcutaneously) with methotrexate	71	39	15	Results at 24 weeks
	Methotrexate alone	27	3	0	
Bathon et al (2000) <sup>6</sup>	Etanercept (25 mg twice weekly, subcutaneously)	72	49	25	Results at 12 months in a group of early, methotrexate naïve, patients
	Methotrexate alone	65	41	2	
Weinblatt et al (2003) <sup>7</sup>	Adalimumab (40 mg every second week, subcutaneously) with methotrexate	67	55	27	ARMADA results at 24 weeks
	Methotrexate alone	14	8	5	

## *Etanercept*

The efficacy of etanercept has been evaluated in three randomised controlled studies. One study randomised 234 patients, whose rheumatoid arthritis had responded inadequately to at least one disease-modifying drug, to receive either placebo injections or etanercept 10 mg or 25 mg subcutaneously twice-weekly for six months. Although methotrexate was not used in this study, the ACR20 and ACR50 responses (Table 1) were similar to the responses to infliximab.<sup>4</sup>

In a more clinically relevant study, 89 rheumatoid arthritis patients with active disease, despite at least six months of methotrexate at doses of 15–25 mg weekly, were randomised to add either placebo injections or twice-weekly etanercept 25 mg for 24 weeks. Although this study was shorter, the ACR20 and ACR70 responses were higher, presumably because of the concomitant use of methotrexate.<sup>5</sup>

The third etanercept study included 632 patients who had suffered rheumatoid arthritis for less than three years, but who had active disease with evidence of bone erosions on X-ray and were rheumatoid factor positive. The patients were randomised to start either methotrexate and placebo injections or placebo tablets and etanercept 10 mg or 25 mg for 12 months. Patients receiving 25 mg of etanercept twice weekly improved more rapidly than the patients taking weekly methotrexate, but by the end of the study the clinical parameters of the two groups were not statistically different.<sup>6</sup>

## *Adalimumab*

The efficacy of adalimumab was evaluated in the ARMADA study in which 271 patients with active rheumatoid arthritis were randomised to receive either 20 mg, 40 mg or 80 mg of adalimumab or placebo injections subcutaneously every second week for 24 weeks.<sup>7</sup> The participants remained on methotrexate treatment. The results were similar to those of treatment with infliximab and etanercept (Table 1).

## ***Disease-modifying effects***

To evaluate the effects of treatment on the progression of rheumatoid arthritis, X-rays of the hands and feet are taken and scored using the modified Sharp method. This scores the severity of the erosions and the narrowing of the joint space of predefined joints.<sup>8</sup> However, the changes in the Sharp score are a surrogate marker for end-points such as joint replacement surgery. Changes in the modified Sharp score occur slowly and therefore only the longer ATTRACT<sup>2</sup> and etanercept<sup>6</sup> studies have evaluated the disease-modifying ability of the TNF- $\alpha$  inhibitors.

In the ATTRACT study the mean change in the modified Sharp score at 54 weeks was an increase (worsening) of 7.0 in the methotrexate alone group and an increase of 1.3 in the group treated with weekly methotrexate and infliximab 3 mg/kg every eight weeks. In the etanercept study the mean increase

in the modified Sharp score at 12 months was 1.0 in the group receiving etanercept 25 mg alone and 1.59 in the group receiving methotrexate alone. The TNF- $\alpha$  inhibitors are, therefore, currently the most significant inhibitors of radiologically-measured joint damage. However, it remains to be proven that a smaller increase in a surrogate outcome results in better functional outcomes.

## **Toxicity of TNF- $\alpha$ inhibitors**

When evaluating the safety of a new drug all sources of information are considered including the randomised and open label studies and post-marketing surveillance. As infliximab and etanercept are powerful immunosuppressive drugs, particular scrutiny needs to be focused on the incidence of infection and malignancy.

Concerns regarding the activation of demyelinating conditions after the use of TNF- $\alpha$  inhibitors have recently been reported. At this stage it would seem prudent to avoid using TNF- $\alpha$  inhibitors in patients with multiple sclerosis and similar conditions.

## ***Infliximab***

In the ATTRACT study there was no difference in the incidence of adverse and serious adverse events or deaths when the methotrexate alone and infliximab-treated patients were compared. Despite this observation, the authors reported marginal numerical increases in the incidence of upper respiratory tract infections, sinusitis and pharyngitis in the infliximab group. Malignancy was reported in five of the infliximab-treated patients, but it is difficult to conclude if these cancers were related to the drug. Infusion reactions occurred in about 20% of the patients given infliximab, but were often mild and required minimal treatment. Recurrent infusion reactions were managed with prophylactic antihistamines, hydrocortisone and/or a slower infusion rate. Antibodies to double stranded DNA (ds-DNA) were significantly more frequent in the infliximab-treated patients, but only one patient developed a rash suggestive of systemic lupus erythematosus (SLE).

In patients treated with infliximab for Crohn's disease, infusion reactions and antibodies to infliximab have reduced the efficacy of the treatment.<sup>9</sup> The same study, however, found that co-administration of other immunosuppressant medications reduced the frequency of these phenomena and therefore improved efficacy. It is therefore a requirement that when infliximab is used in the treatment of rheumatoid arthritis patients it must be given with methotrexate.

The reactivation of tuberculosis was recently reported in 70 patients treated with infliximab for rheumatoid arthritis, Crohn's disease and a variety of other autoimmune conditions.<sup>10</sup> In the majority of cases the tuberculosis developed after three or fewer infusions and 40 of the 70 patients had extra-pulmonary disease. As a result, guidelines to prevent tuberculosis have

recently been promulgated. It is currently recommended that a chest X-ray and Mantoux test be performed before patients start a TNF- $\alpha$  inhibitor. The reported frequency of other opportunistic infections has not increased.

### Etanercept

In the studies of etanercept, the commonest adverse effects attributable to the drug were injection site reactions, occurring in 37–49% of the patients. The frequency of these reactions reduced during each of the studies and their occurrence did not decrease the efficacy of the drug. The frequency of ds-DNA antibodies was increased, but clinical SLE did not develop in any of these patients. Antibodies to etanercept were uncommon. Infections were not increased in the etanercept-treated patients, but it is reasonable to assume that tuberculosis might be reactivated by etanercept so caution should be exercised.

### Adalimumab

In the studies evaluating adalimumab the adverse event profile was similar to that of etanercept and infliximab. It would be anticipated that much of the toxicity reported for the anti-TNF drugs would be related to the TNF inhibitor effect rather than drug-specific effects, with the possible exception of infusion reactions with infliximab.

### Other diseases and biological agents

The inhibitors of TNF- $\alpha$  (including adalimumab, etanercept and infliximab) are currently being evaluated in other forms of inflammatory arthritis including ankylosing spondylitis and psoriatic arthritis. Results of these studies are extremely promising, particularly the improvements in axial disease. A variety of other drugs are being developed to inhibit the action of TNF- $\alpha$ , some of which may be orally bioactive. Inhibitors of other key pro-inflammatory cytokines, including interleukin 1, are also being evaluated. Anakinra, which antagonises interleukin 1 $\alpha$  and 1 $\beta$ , has recently been approved for use in Australia. Some research is examining the effects of combining cytokine inhibitors. All of these studies suggest incremental improvement in the outcomes for patients with severe rheumatoid arthritis. The question for the future is the price we are willing to pay for these incremental improvements.

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### Further reading

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*Associate Professor McColl is a member of the Schering Plough Infliximab Advisory Board in Australia, and is an investigator in studies evaluating the toxicity and efficacy of infliximab and adalimumab.*

### Self-test questions

*The following statements are either true or false (answers on page 51)*

7. To avoid immunosuppression, patients with rheumatoid arthritis should stop methotrexate before starting infliximab.
8. Inhibitors of tumour necrosis factor alpha may reactivate tuberculosis.