

# New drugs in the treatment of RHEUMATOID ARTHRITIS

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*NICE is expected to issue guidance in March on the use of etanercept and infliximab in the treatment of rheumatoid arthritis. These two drugs, as well as some others now being developed, are reviewed below*

**R**heumatoid arthritis (RA) is a chronic systemic inflammatory disease characterised by potentially deforming symmetrical polyarthritis and extra-articular features, which may affect the lungs, kidneys and vasculature. Disease progression results in joint damage, deformation and loss of function, all of which mean disability and a reduction in quality of life.

RA affects approximately 1 per cent of the population. The estimated cost of RA to the National Health Service is £240–600m per year and may be as high as £1.3bn.<sup>1</sup> The social cost of RA is also considerable, with significant numbers of patients being unable to work, requiring residential home care and having reduced life expectancy.<sup>1</sup> Data from the late 1980s suggest that 80 per cent of patients will be disabled after 20 years, although, since the approach to treatment of RA has become more aggressive since that time, the percentage may now be much less.<sup>2</sup>

The initial presentation of newly diagnosed RA patients can be roughly categorised into three distinct groups. The first group, comprising 75 per cent of patients with RA, have a slow onset of disease, approximately 20 per cent have intermediate disease activity and the remaining 5 per cent of patients have a rapidly debilitating illness. Patients in the last category have aggressive disease which is associated with rapid destruction of the joints.

## RESPONSE TO TREATMENT

**R**esponse to treatment in RA patients can be assessed using a number of subjective and objective markers of disease.

One way of measuring response to therapy is to use the American College of

Rheumatology (ACR) guidelines. Patients are scored using various criteria and scores are compared to obtain an improvement in their symptoms. This is referred to as the ACR response (see Panel, p17).<sup>3</sup>

For the purposes of clinical trials, the ACR response is usually used to describe how many patients have a 20 per cent, 50 per cent or 70 per cent improvement in their overall scores which equate roughly to the patient's ability to carry out activities of daily living.

Another way in which the status of RA patients can be determined is by using the Disease Activity Score (DAS 28).<sup>4</sup> This score is calculated using an assessment of 28 joints for swelling and tenderness (hence DAS 28), erythrocyte sedimentation rate (ESR), and patient global assessment of disease activity. A DAS score of 5.1 or greater, suggests highly active RA. A good improvement in DAS score is indicated by a fall of greater than 1.2. A DAS score of 3.2 or less indicates a low level of disease activity.

## CYTOKINES

**C**ytokines are local messengers and signalling molecules. They are involved in the development of the immune system, cell growth and differentiation, repair mechanisms, and the inflammatory cascade. These cytokines may be pro-inflammatory or anti-inflammatory.

Pro-inflammatory cytokines include tumour necrosis factor (TNF) alpha, interleukin (IL)-1, IL-6, and other chemokines. The naturally occurring anti-inflammatory cytokines include soluble TNF receptors (sTNFRs), IL-1 receptor antagonists, soluble IL-1 receptors (sIL-1Rs), IL-4, IL-10, and tumour growth factor (TGF)-beta. Whether patients develop inflammatory signs and symptoms depends on the degree of balance between pro-inflammatory and anti-inflammatory cytokines. The recent and ongoing development of drugs to target these inflammatory mediators has revolutionised the drug treatment of RA.<sup>5</sup>

## TUMOUR NECROSIS FACTOR

**T**umour necrosis factor (TNF) is an important pro-inflammatory cytokine, which is predominantly produced by activated macrophages and monocytes. The effect of TNF on target cells (see Figure on p17) is mediated by receptors on the cell surface and the degree of TNF activity is mediated by sTNFRs, of which there are two subtypes, p75 and p55. These are naturally occurring agents which neutralise the action of TNF. This neutralising action has been explored in the treatment of RA.

## ETANERCEPT

**E**tanercept is a dimeric protein with two sTNFRs fused to a human immunoglobulin. Etanercept binds to TNF-alpha before it can interact with the cell surface receptors. Etanercept is also believed to target TNF-beta (lymphotoxin alpha), which may be important in juvenile idiopathic arthritis.<sup>6</sup> Unlike infliximab, it is not necessary to give etanercept in combination with methotrexate, since antibody formation does not seem to be a problem. Since etanercept has a half-life of 70 hours, it is given by twice-weekly subcutaneous injection.

A phase III randomised controlled trial recruited 234 patients with active disease.<sup>7</sup> These patients had shown an inadequate response to upwards of four disease-modifying anti-rheumatic drugs (DMARDs). All DMARDs were discontinued in these patients one month before treatment with etanercept. Patients were allowed to continue using low dose corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs). Patients were assessed using a variety of parameters, including ACR defined responses at 20 per cent, 50 per cent and 70 per cent. Assessment took place weekly for one month and then monthly for a further five months. Patients were randomised to receive etanercept at 25mg or 10mg twice-weekly, or placebo, via subcutaneous injection.

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### Panel: What is an ACR 20 improvement?

1. Over 20 per cent improvement in tender joint count
2. Over 20 per cent improvement in swollen joint count
3. Over 20 per cent improvement in more than three of the following:
  - Patient pain assessment (using a visual analogue scale)
  - Patient global assessment
  - Physician global assessment
  - Patient self-assessment of disability (using a health assessment questionnaire)
  - ESR or C-reactive protein (CRP)

The results of the trial showed that both doses of etanercept significantly increased the proportion of patients achieving a 20 per cent response at two weeks, three months and six months. In terms of ACR 50 per cent, the 10mg dose achieved significant increases in comparison with placebo at six months only, whereas the 25mg dose achieved these increases for all three time frames. For ACR 70 per cent, the 10mg dose did not offer significant increases over all time periods. However, the 25mg dose achieved increases at three months and six months. A number of other disease markers were reduced significantly over the treatment period, including quality of life and tender and swollen joint scores.

The authors concluded that etanercept was a well tolerated and effective treatment for active RA, resulting in a significant improvement in a number of disease-related parameters. They also concluded that the 25mg twice-weekly dose was significantly superior to the 10mg dose without any significant decreases in tolerability. Patients from this study were eligible to enter a long-term open-label study and data have shown efficacy and safety over four years.<sup>8</sup>

Etanercept has also been evaluated in children with polyarticular juvenile rheumatoid arthritis.<sup>9</sup> Patients enrolled into the study were aged between four and 17 and had active polyarticular juvenile rheumatoid arthritis despite treatment with NSAIDs and/or methotrexate. The use of DMARDs was discontinued in patients who were taking them before the study began. In the initial open-label part of the trial, all 69 patients received 0.4mg per kg of etanercept

up to a maximum of 25mg. Patients were assessed three months into the study, and those who had met the improvement criteria were randomised to receive either etanercept or placebo as part of a double-blind study. These patients continued on this

regimen until four months had elapsed or until their disease flared up. Patients were assessed using a number of methods, similar to those described earlier. Of all 69 patients, 44 (64 per cent) met the criteria for 50 per cent improvement and 25 (36 per cent) met the criteria for 70 per cent improvement. At the end of the open-label study, 51 patients (74 per cent) had met the criteria for improvement, with improvement noted as early as two weeks in some patients. These 51 patients then entered the double-blind phase of the study, with 25 patients receiving etanercept while the rest were put on placebo. It was found that 21 (81 per cent) of the 26 patients receiving placebo experienced disease flare, when compared with seven (28 per cent) patients of the 25 patients who received etanercept, a significant difference ( $P=0.003$ ).

At the end of the seven-month study, 20 (80 per cent) of the 25 patients receiving etanercept met the definition of improvement in comparison with nine (35 per cent) of the patients receiving placebo ( $P<0.01$ ). Also, of the patients receiving etanercept, 18 (72 per cent) met the definition for 50 per cent improvement and 11 (44 per cent) met the definition for 70 per cent improvement, compared with six (23 per cent) and five (19 per cent), respectively, in patients receiving placebo. Overall, etanercept was well tolerated by the patients receiving it. Of the 68 eligible patients in the study, 59 (87 per cent) chose to continue treatment with etanercept in an open-label extension study. The authors of the study concluded that etanercept was well tolerated and resulted in significant improvement in this group of patients.

Another study involving 632 patients compared etanercept with methotrexate over a 12-month period.<sup>10</sup> The patients received either etanercept injections, 10mg or 25mg with placebo tablets, or placebo injections with weekly oral methotrexate. As in other trials, DMARDs were discontinued four weeks before the start of the study. However, NSAIDs and low dose prednisolone (10mg or less per day) were permitted. Clinical end points were again the ACR criteria and radiological data. Also, as in the previously described study, the 25mg dose appeared to have significantly superior efficacy in terms of ACR 20 per cent, 50 per cent and 70 per cent. In terms of the ACR responses, etanercept demonstrated a more rapid onset of action than methotrexate and demonstrated significant benefits during the first six months. However, over six to 12 months, the benefits of etanercept did not appear to be significantly better superior to those of methotrexate. Etanercept had a significantly better effect on erosion scores at six and 12 months, although differences in joint space narrowing were not as clear.

Since raised TNF concentrations have been identified in the joints and skin of patients with psoriatic arthritis,<sup>11</sup> etanercept has been evaluated in the treatment of such patients. In a 12-week study, the safety and efficacy of etanercept was evaluated in 60 patients randomised to receive either etanercept 25mg twice-weekly or placebo. The results of the trial showed that all markers of joint disease were significantly reduced in patients treated with etanercept and improvements in psoriatic lesions were superior in the etanercept group. Although the trial was small in size and of short duration, the results suggest that etanercept significantly improves disease parameters in these patients and could offer a new option in the treatment of psoriatic arthritis.

## INFLIXIMAB

Infliximab is a chimeric monoclonal antibody. It combines mouse and human immunoglobulins in an effort to reduce the antigenicity of the agent. Infliximab inactivates free and bound TNF and prevents it from activating cell surface receptors. Since infliximab has a half-life of about 200 hours, it may be administered every eight weeks once a maintenance dose is reached. Initiation of infliximab therapy is achieved by giving an initial dose, followed by further doses at weeks two, six and 14, and maintenance doses at eight-weekly intervals thereafter.

In one study, 428 patients receiving concurrent methotrexate were randomised to receive either placebo or infliximab at a dose of either 3mg per kg or 10mg per kg over a 54-week period at either four or eight-weekly intervals.<sup>12</sup> Response to therapy was

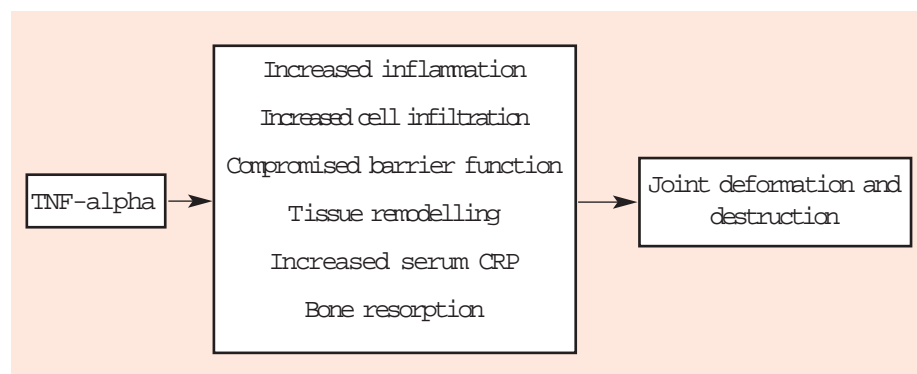


Figure: Role of TNF-alpha in joint deformation and destruction

assessed using ACR targets of 20 per cent, 50 per cent and 70 per cent. Assessments of functional ability were carried out and markers of inflammation measured. Radiological images of the hands and feet were also examined. Overall, patients receiving infliximab at the 3mg per kg and 10mg per kg doses did not have significantly differing responses, hence the current dosing regimen is 3mg per kg. Significant differences between ACR responses were seen between the infliximab-treated patients and those receiving placebo.

The trial demonstrated that infliximab and methotrexate prevented further joint damage whereas the placebo and methotrexate group had measurable increases in joint damage. In addition, patients receiving infliximab reported superior scores for quality of life and measurement of inflammatory markers. Joint damage was prevented in patients receiving infliximab regardless of whether they had a clinical response or not, suggesting that the drug has activity above that of reduction in clinical symptoms. In some patients, joint damage appeared to have been repaired.

## GUIDELINES

Since the drugs described here are new and expensive, guidelines to support their use have been formulated by the British Society of Rheumatology.<sup>13</sup> There are four key areas for consideration.

First, patients must have active RA, defined using the criteria described earlier with the DAS 28 score favoured by the working party.

Second, patients must have failed "adequate therapeutic trials" of at least two standard DMARDs, of which methotrexate must be one. Adequate therapeutic trials are defined as at least six months' treatment with at least two months at standard target doses (unless limited by toxicity) or for less than six months if treatment was withdrawn due to intolerance or toxicity and at least two months of therapeutic doses was administered.

Patients should not be treated if they meet any of the exclusion criteria listed in the summary of product characteristics, for example, active infection, pregnancy and breast-feeding.

Finally, the guidelines give criteria for cessation of treatment, for example, with regard to adverse events, malignancy, severe intercurrent infection or lack of efficacy.

## TRIAL DATA

The efficacy of anti-TNF agents is not in question. The trials described above have shown that these agents (with or without methotrexate), are superior to methotrexate alone in the treatment of RA. (Methotrexate is regarded as the gold standard treatment for RA.) However, further research is required

to investigate the effects of these agents relative to, or when combined with, other DMARDs and combinations of DMARDs.

Data from trials suggest that between 25 and 40 per cent of patients will fail to respond to infliximab or etanercept therapy. It is unclear why this is the case, and future work may identify possible reasons.

## SAFETY AND EFFICACY

The main aspects of safety that have been studied include the tendency of anti-TNF agents to cause cancer and to stimulate antibody formation.

**Carcinogenicity** Trials investigating the incidence of neoplasia have been limited by their duration and the numbers of patients involved. It is worth noting, however, that the neoplasms identified in these patients tend to be blood-borne tumours rather than solid tumours. The effects of the drug appear to be reversed once the drug is withdrawn. This presents something of a problem since the long-term safety of the drug has not yet been established.

Recently, concern has centred on central nervous system demyelinating disorders. The relationship between TNF-alpha and multiple sclerosis and related signs and symptoms (for example, optic neuritis or dysaesthesia) is unclear and caution should be exercised.<sup>14</sup>

The use of infliximab in patients with heart failure has also generated some safety concerns. An interim report of a phase II trial with infliximab in patients with heart failure found that seven of the 101 patients treated with infliximab died during the study, compared with none of the 49 patients receiving placebo.<sup>15</sup> The manufacturers advise that the use of infliximab in patients with heart failure who are already receiving therapy should be reviewed appropriately.

**Effects of antibody formation** Infliximab is derived from human and mouse immunoglobulins. This combination is an attempt to reduce the antigenicity of the agent. Since antibody formation is a problem, the drug is given concurrently with methotrexate so as to prevent the formation of infliximab antibodies. In addition, non-neutralising antibodies to etanercept have been identified.<sup>9</sup>

Formation of anti-double stranded DNA (anti-dsDNA) antibodies and antinuclear antibodies is found to be increased with both infliximab and etanercept. The presence of anti-dsDNA antibodies can lead to clinical signs and symptoms consistent with a lupus-like syndrome in rare instances. In patients treated with infliximab and who developed an increase in concentrations of these antibodies, a return to normal anti-dsDNA levels was noted when the drug was discontinued.

**Susceptibility to infection** Anti-TNF-

alpha agents affect host response to infection, and in trials have shown that infections (predominantly upper respiratory tract infections) are more commonly seen in those taking anti-TNF-alpha compared with placebo. Based on 70 reports to the Food and Drug Administration in the United States, there are particular concerns about the development of active tuberculosis after initiation of treatment with infliximab.<sup>16</sup> The manufacturer recommends that patients should be screened for latent or active tuberculosis before treatment with infliximab. The association between etanercept and tuberculosis is less clear, but similar caution is advisable. In patients who have an increased susceptibility to infection, or in whom recurrent infections occur, caution should be exercised when using anti-TNF agents.

## FURTHER STUDIES

While there is no doubt that the trials examining the use of anti-TNF agents are of an appropriate quality, a number of concerns exist. Most were relatively small in number and of short duration. Since RA is a chronic disease and trials suggest that the treatments need to be continued to receive sustained benefits, the long-term studies that are needed to evaluate the safety of these agents are either ongoing or are due to be published in the near future. The advent of IL-1 receptor antagonists provides the additional option of blocking the effects of both TNF-alpha and IL-1. This combination can be used as a last resort for patients who have failed to benefit from anti-TNF and IL-1 therapies alone, for example, in the treatment of patients with intractable RA.

## FUNDING ISSUES

NICE is currently reviewing the use of anti-TNF agents in RA, and the expected date of final guidance is March 2002.<sup>17</sup> The potential cost to the NHS of treating all eligible patients is considerable. However, from a broader perspective, TNF-specific therapy has a large number of potential benefits, including a reduction in social support, delaying or avoiding joint replacements, reduction in costs related to sickness absence from work and a reduction in hospital admissions.

## DRUGS OF THE FUTURE

Adalimumab is a monoclonal anti-TNF antibody that is expected to be on the market in 2002.<sup>19</sup> It is the first anti-TNF antibody that is entirely human in origin. For this reason, it is expected that patients will be able to tolerate the drug for longer, antibody formation will be less likely, and there should be fewer allergic reactions. Adalimumab is given every other week, and is administered via the subcutaneous route.

Anakinra is another new agent which

*Table: Comparison of etanercept and infliximab*

	<b>Etanercept</b>	<b>Infliximab</b>
Licensed indications <sup>1</sup>	RA in adults failing to respond to at least two DMARDs, including methotrexate. Polyarticular course juvenile chronic arthritis in children.	RA in adults with inadequate response to DMARDs, including methotrexate. Infliximab is only licensed for use in combination with methotrexate. Severe, active or fistulising Crohn's disease in patients failing to respond to conventional therapy.
Half life	70 hours	200 hours
Dose	Adults, including the elderly, 25mg twice-weekly. Children: 0.4mg per kg (maximum 25mg) twice-weekly	3mg per kg at weeks zero, two, six, 14 and then eight-weekly thereafter
Route of administration	Subcutaneous injection	Intravenous infusion
Renal or hepatic impairment	No dosage adjustment required	No information
Cost of vials <sup>18</sup>	Four 25mg vials — £325.00	100mg vial — £451.20
Cost of 54 weeks' treatment <sup>3</sup>	£8,775	First year: £8,121.60–12,182.40

1. For detailed descriptions, see summaries of product characteristics.
2. Etanercept may be given once-weekly but this may result in a slower response and reduced efficacy.
3. Costs for etanercept based on twice-weekly injections of 25mg. Costs for infliximab based on initiation of treatment and injections at weeks zero, two, six, and then eight-weekly until week 54. Range of costs based on patients requiring either two or three vials per dose.

will be marketed in the next few years. Anakinra's actions are not directly related to TNF since the drug is a recombinant form of IL-1RA. Data are currently limited to small trials but it is expected that further information will be forthcoming.<sup>20,21</sup> Since Anakinra has a mode of action which differs from that of TNF antagonists, the possibility of combination therapy exists.

## SUMMARY

Infliximab and etanercept have been described by patients as "wonder drugs" for the treatment of RA. This is not surprising, considering the overwhelming response that some patients display towards these drugs. The choice of which one of these drugs to use in RA is influenced by patient preference and, in the short term, by the availability of adequate supplies of the agents themselves. Some patients prefer to self-administer (etanercept) while others prefer to visit their rheumatology unit for an infusion (infliximab). The two drugs are compared in the Table.

The cost of these agents is considerable, but given the effects and impact of RA on patients, these treatments often represent new and effective options for many patients. While etanercept and infliximab are the only biological agents currently licensed for RA, there will be a number of additional agents available in the near future. Differences in mode of action and administration allow RA patients and those involved in

their care to have a number of new and effective options in managing the disease.

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