

USING TNF α TECHNOLOGY TO TREAT RHEUMATOID ARTHRITIS

By CHRIS GREEN, PhD, MRPHARMS

Biopharmaceutical products against TNF α are increasingly being used to treat rheumatoid arthritis. This article explores the technology behind these products and examines their current and future role

X-ray of the hands of a person with rheumatoid arthritis

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Advances in technology have led to biopharmaceutical products being developed to target tumour necrosis factor-alpha (TNF α), a cytokine (ie, signalling molecule) with a key role in the pathology of inflammatory disorders. The specificity of anti-TNF α products, together with the fact that they modify the disease process (rather than just treat symptoms) makes them useful agents in the treatment of rheumatoid arthritis. However, as with many other biopharmaceutical products, the high level of technology involved in their development is reflected in their relatively high costs to the NHS.

This article aims to give an overview of the key anti-TNF α products launched to date (etanercept, infliximab and adalimumab), highlighting aspects of the science behind them and discussing some financial issues. Recent National Institute for Clinical Excellence (NICE) guidelines are described, as are some other anti-inflammatory biopharmaceutical products.

ROLE OF TNF α

TNF α is predominately produced by activated macrophages, monocytes, B cells and T cells. It is believed to be involved in a

wide range of processes in the immune system, including:

- Stimulating the production of other pro-inflammatory cytokines such as IL-1^{1,2}
- Stimulating leucocyte trafficking to joints²
- Stimulating the production of "vascular permeability factor", an agent that is believed to contribute to joint swelling²

Its effects are mediated by TNF α receptors on the surface of target cells. Naturally occurring soluble TNF α receptors (of which there are two sub-types — p75 and p55) modulate its activity in the body.

ETANERCEPT

Etanercept consists of two soluble recombinantly produced TNF α p75 receptors (see above) fused to the constant region of IgG1. The receptor component of the product binds to free TNF, thereby preventing TNF from interacting with the TNF α receptor site on target cells and propagating an inflammatory response. The antibody component has no real therapeutic activity — it increases the half life of the product to approximately 70 hours (the TNF α p75 receptor alone has a half life of approximately four hours only). The dimeric nature of the product increases the potency of TNF α inhibition. Etanercept is also thought to target Tumour Growth Factor- β , the significance of which is the subject of further investigation.

The findings from a number of trials demonstrating the safety and efficacy of etanercept have been published over the past few years.^{3,4} Much of these data were discussed in a 2002 *Hospital Pharmacist* special feature on rheumatoid arthritis.⁵ Since then, the results of the TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study have been published. In the study, approximately 230 patients in each group received either etanercept, methotrexate or a combination of the two. The combination of methotrexate and etanercept showed a significant reduction in disease activity, improvement in functional disability and slowing of radiographic progression. At week 52, 43 per cent of patients in the combination group achieved an ACR70 response (see panel 2, p289), compared with 19 per cent and 24 per cent in the methotrexate and etanercept groups' respectively.⁶

Etanercept is given subcutaneously, conventionally as a 25mg dose twice weekly. More recently, the use of 50mg once weekly, has been suggested as an equivalent dosing schedule.⁷

INFLIXIMAB

Infliximab is a chimeric monoclonal antibody (See Figure 1, p287) that binds to and neutralises the effects of both free and bound TNF α .

As with etanercept, the safety and efficacy of infliximab has been demonstrated in a number of clinical trials,⁸ and much of these data have already been discussed in

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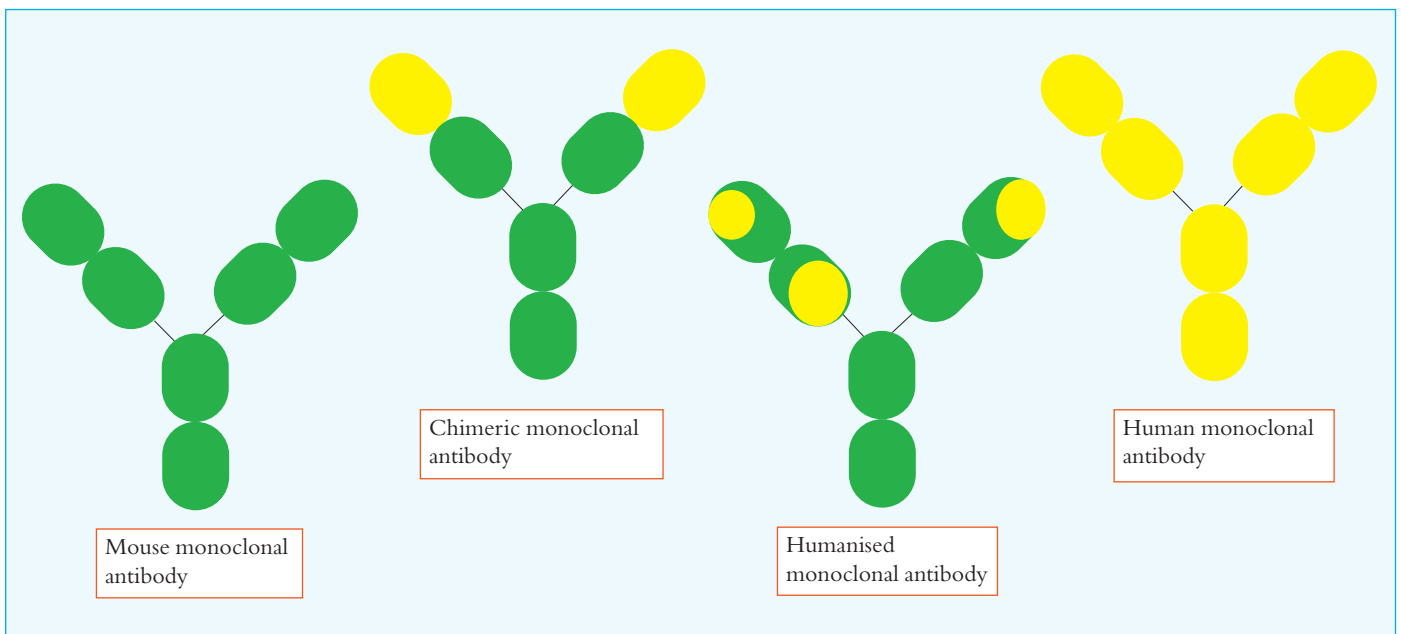


Figure 1. The different types of monoclonal antibodies. Antibody material containing mouse genetic sequence is shown in green and antibody containing human genetic sequence is shown in yellow. Immunising a mouse with an appropriate antigen produces a mouse monoclonal antibody. Further manipulation can result in a chimeric or humanised molecule. Techniques such as culturing the fully human gene sequence of the antibody in Chinese hamster ovary cells or altering the genetic make-up of the mouse so that it contains human chromosomes can be used to produce fully human monoclonal antibodies

*Hospital Pharmacist.*⁵ Since that time, interest has grown in the intra-articular use of infliximab. Doses of 100mg, 24h apart, have been used to treat patients in whom inflammation in one joint is causing particular concern.⁹

There is increasing anecdotal evidence that the dose of infliximab currently licensed (3mg/kg given every eight weeks, once patients are through the induction phase) is insufficient for some patients and

so a strategy of either increasing the dose, reducing the dosing interval or both, has been employed. Such strategies clearly affect the overall costs of infliximab therapy.

ADALIMUMAB

Adalimumab, a fully human monoclonal antibody against TNF α , was first marketed in autumn 2003. It is presented as a pre-filled syringe and is administered (subcutaneously) fortnightly (although weekly doses may be necessary for certain patients).

Several clinical trials investigating the safety and efficacy of adalimumab have been carried out. In the ARMADA (Anti-tumour necrosis factor Research study program of the Monoclonal Antibody aDalimumab in rheumatoid Arthritis) study, the effects of the fortnightly administration of three different doses (20mg [n=69], 40mg [n=67] and 80mg [n=73]) of adalimumab in combination with methotrexate were compared with the effects of placebo in combination with methotrexate [n=62]. A higher percentage of patients who were receiving the 40mg dose reached "ACR20", "ACR50" and "ACR70" (see Panel 2, p289) after 24 weeks of treatment than those who received the other doses. In addition, approximately one quarter of patients taking adalimumab at any dose reached "ACR20" within one week, suggesting that the benefits of treatment are rapidly obtained.¹⁰

In the STAR (Safety Trial of Adalimumab in Rheumatoid arthritis) study, 636 patients were randomly assigned to receive either 40mg adalimumab subcutaneously every other week or a placebo. The frequency of a variety of adverse events was recorded, as were ACR responses. No significant differences in the frequency of adverse events was noted between patients using adalimumab and those receiving the placebo but, after 24 weeks of therapy, a higher proportion of patients receiving adalimumab achieved "ACR20", "ACR50" and "ACR70" than those receiving placebo (52.8 per cent compared with 34.9 per cent; 28.9 per cent compared with 11.3 per cent and 14.8 per cent compared with 3.5 per cent, respectively).¹¹

COMPARING AGENTS

The efficacy of etanercept, infliximab and adalimumab have not yet been investigated in the same trial and so direct comparisons between the agents cannot readily be made. However, the results of the separate trials seem to suggest that the three drugs have a similar efficacy. Post-marketing experience is clearly less for adalimumab than it is for etanercept and infliximab.

A comparison of the costs of treating patients with etanercept, infliximab or adalimumab, based on prices taken from the April 2004 Monthly Index of Medical Supplies, is shown in Panel 1.

SIDE EFFECTS

Antibody formation The production by the immune system of antibodies against an anti-TNF α drug can cause serious allergic

Panel 1: Approximate costs to the NHS of treating patients with etanercept, infliximab and adalimumab

Etanercept Four vials cost £357.50, meaning that the approximate cost to the NHS per patient per year (assuming a fortnightly dosing schedule) is £9,295

Infliximab Each vial costs £451.20, meaning that the approximate cost to the NHS per patient per year is £5,865 or £8,798 depending on whether or not the patient weighs more than 67kg. Costs for the first year of treatment could be higher, because an induction phase is required

Adalimumab Two syringes cost £715, meaning that the approximate cost to the NHS per patient per year is £9,295 or £18,590, depending on whether a weekly or fortnightly dose is needed

Unit prices are those set out in the April 2004 edition of MIMS. For hospitals, VAT needs to be added to the costs quoted, except where delivery is via a home care service provider

reactions (as well as, for example, reduce the efficacy of the therapeutic agent concerned). Antibody formation has been associated with all three anti-TNF α drugs, but seems to be more of an issue with infliximab.¹²

Co-administration of methotrexate reduces the risk of antibody formation. Infliximab must be given in combination with methotrexate therapy.^{12,13} Adalimumab should be given with methotrexate, but can be given as monotherapy if the use of methotrexate is unsuitable for a particular patient.¹⁴ Etanercept can be given as monotherapy, but it has recently been licensed for use with methotrexate.¹⁵

TNF α blockade may also (rarely) result in the development of an autoimmune process with symptoms similar to those seen in lupus.

Infection TNF α is a messenger in the immune response cascade, and so its blockade has the potential (in theory, at least) to make patients more susceptible to infections. It is therefore advisable to monitor patients receiving anti-TNF α drugs for the development of serious or opportunistic infections. In particular, patients with active tuberculosis should not generally be prescribed anti-TNF α drugs and those with inactive or latent tuberculosis should be prescribed prophylactic antibiotics if such therapy is considered appropriate.^{13,14} (These precautions are not listed in the Summary of Product Characteristics for etanercept but in practice, they are often exercised.) Monitoring should continue for some time after therapy is discontinued — infliximab can take up to six months and adalimumab up to five months to clear from the body once treatment has been stopped.¹³

It is important to note that TNF α blockade can mask the symptoms of infection.

Neoplastic disease The influence of TNF blockade on the incidence of neoplastic disease has yet to be fully evaluated and the ongoing monitoring of patients in connection with this issue is therefore important.

Heart failure There have been several reports of new or worsening heart failure associated with TNF α blockade. It is difficult to establish conclusively whether there is a causal association because the underlying frequency of heart failure in patients with rheumatoid arthritis is not known. (Patients with rheumatoid arthritis are known to be at an increased risk of cardiovascular disease, so it would be inappropriate to use the incidence of heart failure in the general population as a comparator.) However, the fact that heart failure symptoms resolved or improved when patients stopped taking anti-TNF α therapy suggests that there may be an increased risk.¹⁶

An association with heart failure is a surprising finding because concentrations of TNF α are raised in patients with heart failure (although heart failure is not an inflammatory process).

Demyelinating and neurological reactions Neurological and demyelinating reactions (exacerbation or development of new onset multiple sclerosis or instances of less specific neurological damage) have been reported in association with infliximab, etanercept and adalimumab.¹⁷ Again, this is a surprising finding because anti-TNF α agents might be expected to be beneficial in autoimmune diseases such as multiple sclerosis.

NICE GUIDELINES

NICE guidelines on the use of anti-TNF α drugs were published in March 2002.¹⁸ Adalimumab was marketed after this date, and so was not included in the analysis.

The guidelines recommend that patients should meet the following criteria before being considered for treatment with anti-TNF α agents:

- Have an ACR diagnosis (ie, meet the criteria set by the American College of Rheumatology)

- Have a high disease activity, indicated by a "DAS 28" score (see Panel 2 below) of greater than 5.1
- Have failed to respond to at least two courses of standard therapy using two disease-modifying agents for not less than six months at the target doses suggested by the British Society for Rheumatology

In addition, NICE recommend that treatment should be withdrawn if no benefit is received after three months, or if the "DAS 28" score does not fall below 3.2 or decrease by 2.1. The NICE guidelines are essentially based on those produced earlier by the British Society for Rheumatology.¹⁹

ANAKINRA

Other recent advances in treating rheumatoid arthritis include the use of anakinra, a recombinantly produced antagonist of the IL-1 receptor. IL-1 is produced by monocytes, macrophages, endothelial cells, B cells and activated T cells and stimulates matrix metalloproteinases from fibroblasts and chondrocytes. Animal studies have implicated excess IL-1 in joint damage, and neutralisation of IL-1 in a reduction in joint damage.¹²

Clinical trials examining the efficacy of anakinra have shown some encouraging

results,^{20,21} although further studies are expected. Because anakinra has a different mode of action to the anti-TNF α agents, the possibility of improving patient outcomes by using combination therapy exists. However, the most significant combination therapy trial suggested that patients taking anakinra in combination with etanercept were at an increased risk of serious infections and neutropenia compared with those taking etanercept alone, with no increase in efficacy.²² Should future trials dispute this finding, or should other combinations prove more beneficial, the cost implications of combination therapy will need to be addressed.

NICE has appraised anakinra and has not approved its use, except in clinical trials or where patients are already receiving the drug and are benefiting from it in such a way that to stop treatment would be inappropriate.²³

ON THE HORIZON

Approximately 25 to 35 per cent of patients do not gain an adequate response to anti-TNF α therapy. There is emerging evidence and anecdotal reports that changing anti-TNF α agent may be of benefit, although the reasons why this approach works are not yet known. Should these options fail, alternatives to the

currently licensed medicines are emerging. Information on these treatments under development is set out below.

Rituximab Rituximab (MabThera) is a genetically engineered monoclonal antibody (against CD20) that depletes B-lymphocytes. It was first investigated as a treatment for rheumatoid arthritis because a patient being treated with it for non-Hodgkin's lymphoma had a coincidental remission of inflammatory arthropathy.²⁴ In a small open label study of patients who received rituximab in combination with other immunosuppressants, all five achieved an "ACR50" response at six months, with three achieving "ACR70".²⁵ Although patients relapsed as their B lymphocyte counts rose, they could be successfully retreated with rituximab. Further work has been undertaken²⁶ and, if progress is maintained, rituximab could be launched as a treatment for rheumatoid arthritis in 2006-7.

CDP870 CDP870 is a genetically engineered human anti-TNF α antibody fragment attached to polyethylene glycol (which extends the half life of the product to approximately 14 days).

A dose-escalating phase II clinical trial compared the efficacy of CDP870 at doses of

Panel 2: Methods used to measure response to therapy in patients with rheumatoid arthritis

Disease Activity Score ("DAS 28")

Disease activity scores are based on the proportion of 28 joints which are tender and swollen, plus markers indicating the patient's quality of life and the degree of inflammation. This score was used as a measure in the British Society of Rheumatology and NICE guidelines

American College of Rheumatology (ACR) response

ACR is a composite measure of the improvement in symptoms in patients with rheumatoid arthritis, used in most clinical trials. It is usually reported as an "ACR20", "ACR50" or "ACR70" response. For example, an "ACR20" response suggests a:

- 20 per cent improvement in tender joint count
- 20 per cent improvement in swollen joint count
- 20 per cent improvement in at least three of the following five assessments:
 - Patient pain assessment (using VAS)
 - Patient global assessment
 - Physician global assessment
 - Patient self assessment of disability (using a HAQ assessment)
 - Biochemical tests (ie, ESR or CRP)

"NICE" means National Institute for Clinical Excellence, "VAS" means visual analogue score, "HAQ" is a health assessment questionnaire. "ESR" is erythrocyte sedimentation rate and "CRP" is c-reactive protein.

1, 5, or 20mg/kg (given as a single infusion, followed by the opportunity of an open label infusion of either 1, 5 or 20mg/kg) with placebo.²⁷ The authors concluded that from the results of this small study, CDP870 was effective and well tolerated. Phase III clinical trials are ongoing. In particular, the results suggest that CDP870 might have a higher response rate than other anti-TNF α agents. Clearly, larger and longer term studies and direct comparisons will need to be carried out before its role as a treatment for rheumatoid arthritis can be established.

CTLA4Ig Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4Ig) blocks one of two signals required for full T-cell activation — activated T-cells are thought to have an important role in the pathogenesis of rheumatoid arthritis. Trials have shown that patients receiving 10mg/kg of a genetically produced CTLA4IG had a better outcome (as defined by the proportion achieving “ACR20” responses) than those receiving 2mg/kg or a placebo.²⁸ However, as with other anti-TNF α therapies, approximately one third of patients did not seem to respond to this treatment at the dose they were given.

Eculizumab Eculizumab is a humanised monoclonal antibody that prevents cleavage of the human complement component C5 into its pro-inflammatory components.²⁹ It has recently completed phase IIb clinical trials, the results of which are yet to be published.³⁰

MRA MRA is a humanised antibody against interleukin-6 (IL-6). IL-6 is a pro-inflammatory cytokine that has a number of roles including T-cell activation and the induction of the acute phase of the inflammatory response. Clinical studies using the agent are under way.³¹

EXPANDING USES

Rheumatoid arthritis is just one of several inflammatory disorders where blocking TNF α is expected to be beneficial. Information about the effects of anti-TNF α therapy in some of these conditions is set out below:

Ankylosing spondylitis Etanercept is licensed for treating ankylosing spondylitis. In a recent trial of 300 patients, almost 60 per cent of those who were randomised to receive etanercept achieved an “ASAS20” response (a similar concept to an “ACR20” response) after 12 and 24 weeks of therapy compared with less than 30 per cent of those receiving placebo.³² Infliximab has also recently been licensed for this use. Anti-TNF α therapy is particularly important in ankylosing spondylitis because, in general, only supportive measures, as opposed to inhibition of disease progression, have previously been available.

Psoriatic arthropathy Etanercept is licensed for the treatment of psoriatic arthritis. In an early trial of 60 patients, those using a 25mg dose of enterecept twice weekly were more likely to achieve a 75 per cent improvement in both the joint symptoms (measured using psoriatic arthritis response criteria and ACR responses) and the psoriatic symptoms (measured using a psoriasis area and severity index) of their disease than patients receiving a placebo, with no significant differences in the incidence of adverse events.³³

A small study has shown infliximab to be effective in improving psoriatic symptoms, but less so in improving the joint symptoms, of patients with psoriatic arthritis. Some toxicity issues were, however, evident.³⁴

Vasculitis Infliximab has shown some promise in the treatment of vasculitic conditions (such as Wegener’s granulomatosis), although the case reports have so far been few and usually from short term studies.³⁵

Patients with clinically problematic vasculitis have previously been treated with immunosuppressants (usually high dose corticosteroids and cyclophosphamide), which can be difficult to tolerate, and so the use of anti-TNF α agents, although their long-term side effects are not known, could offer significant benefits.

Churg-Strauss-Syndrome (a systemic disorder characterised by asthma, pulmonary infiltrates and vasculitis) has also been successfully treated with infliximab and etanercept.³⁶

CONCLUSION

Anti-TNF α drugs have been shown to offer considerable benefits in the treatment of rheumatoid arthritis in many patients whose disease has not been adequately controlled with other agents or where the side effects of other agents (such as those associated with the prolonged use of cyclophosphamide and high-dose corticosteroids) have limited treatment.

The cost of treating patients with etanercept, infliximab or adalimumab is considerable. It must not, however, be forgotten that the effective treatment of rheumatoid arthritis can prevent the need for, for example, surgery or physiotherapy treatment, and so the use of expensive drugs can be a cost-effective option in this context. Such drugs can also markedly improve a patient’s quality of life.

While the anti-TNF α drugs and anakinra are the only biopharmaceutical agents currently licensed for treating rheumatoid arthritis, there are likely to be a number of additional agents available in the future. These will be of particular interest to the 25–35 per cent of patients who do not respond particularly well to the currently available anti-TNF α agents.

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Other advances in the treatment of rheumatoid arthritis

Readers interested in this article might also like to note that there is renewed interest in methotrexate, one of the older drugs used in rheumatology.

Although methotrexate is considered by many to be the “gold standard” disease modifying agent for rheumatoid arthritis, treatment often needs to be withdrawn because of poor tolerance. To counter this, and also to aid absorption, an increasing number of patients are being treated with intramuscular or subcutaneous methotrexate. For example, clinicians at Leeds Teaching Hospitals NHS Trust have recently advocated using parenteral methotrexate before patients are considered for biopharmaceutical therapies.

More details about this strategy are available from: Bingham SJ, Buch MH, Lindsay S, Pollard A, White J, Emery P. Parenteral methotrexate should be given before biological therapy. *Rheumatology* 2003;42:1009–10.

NICE to appraise adalimumab

Adalimumab is included in the 10th wave of National Institute of Clinical Excellence technology appraisals. At the time of *Hospital Pharmacist* going to press, the expected date of publication was unknown. See p263 for details about other disease areas and drugs to be appraised by NICE.

Annual European Congress of Rheumatology

Scientists and health care professionals from 93 countries met last month in Berlin to discuss advances in the management of rheumatic diseases. Recent discoveries about genetic predisposition were also discussed. A meeting report from the conference was published in *The Pharmaceutical Journal* (2004;272:818–9) and is available via www.pjonline.com/links/hp