Tumour necrosis factor inhibitors

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ABSTRACT

- The cytokine, tumour necrosis factor-alpha (TNF-α) plays a key role in the pathogenesis of many chronic inflammatory and rheumatic diseases, in particular, Crohn's disease, rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis.
- Controlled trials have shown that the TNF inhibitors (etanercept, infliximab and adalimumab) significantly reduce symptoms and signs, improve function and quality of life, and reduce radiologically evident damage in patients with rheumatoid diseases. For reasons that are not entirely clear, etanercept does not work in Crohn's disease.
- Injection site and intravenous reactions and increased risk of infection (in particular, reactivation of tuberculosis) are associated with the use of these agents.
- Increased risk of lymphoproliferative disease, the development of lupus-like syndromes and demyelination, including optic neuritis and reactivation of multiple sclerosis, are under evaluation in long-term follow-up studies.
- The TNF inhibitors are expensive (about $18 000 per year), and in some patients need to be given continuously to maintain benefit, even in the presence of other immunosuppressive therapy.

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Although the triggering factors for many autoimmune diseases are not known, one of the key inflammatory mediators in the attending chronic inflammatory process is the cytokine, tumour necrosis factor-alpha (TNF-α).[1] TNF-α overexpression acts as a driver for inflammation that damages cartilage, bone and bowel mucosa, and TNF-α inhibition leads to significant clinical improvements and reduction of this damage. Three TNF-α inhibitors are currently listed by the Pharmaceutical Benefits Scheme (PBS) for use in Australia, in instances of severe disease uncontrolled by other disease modifying measures. They are:

- infliximab — an IgG_1 monoclonal antibody (a chimera of human constant and mouse variable regions), for use in rheumatoid arthritis, ankylosing spondylitis and Crohn's disease;
- etanercept — a fusion protein of human IgG and two p75 TNF receptors, for use in rheumatoid arthritis and ankylosing spondylitis (awaiting approval for use in psoriatic arthritis); and
- adalimumab — a humanised IgG_1 monoclonal antibody (fully human constant and variable regions), for use in rheumatoid arthritis.

A number of similar agents are under active development. These include a pegylated anti-TNF-α (pegylation adds polyethylene glycol to a protein to prolong its half-life) combined with the p55 receptor for TNF-α.

Infliximab binds to TNF-α and TNF-β and lyses TNF-producing cells to neutralise their activity.[2] It is licensed for use in combination with weekly low-dose methotrexate therapy in rheumatoid arthritis, and is given by intravenous infusion at baseline, 2 weeks, 6 weeks, and thereafter 8-weekly. The dose is 3 mg per kilogram in rheumatoid arthritis and 5 mg per kilogram in ankylosing spondylitis and psoriatic arthritis (Box 1). In Crohn's disease, it is approved for acute and maintenance therapy and the dose is 5 mg per kilogram (Box 1). The presence of murine sequences is associated with the formation of anti-chimeric antibody production, which can result in infusion reactions and a reduction in efficacy with long-term therapy, although the rate of discontinuation of treatment for this reason is less than 2%.[3]

Etanercept is a recombinant dimer of human TNF receptor proteins fused and bound to human IgG_1 that acts competitively to inhibit the binding of TNF to its cell surface receptor. It is given by subcutaneous injection 25 mg twice weekly. Studies have shown that 50 mg given once a week has equal efficacy to twice-weekly injections in patients with rheumatoid arthritis.[4]

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For reasons that are not entirely clear, etanercept is not effective in Crohn's disease.

Adalimumab is a monoclonal fully human anti-TNF-α antibody that binds with high affinity to TNF-α. It is approved for treating rheumatoid arthritis both in combination with methotrexate and as monotherapy. It is given by subcutaneous injection at a dose of 40 mg every 2 weeks. By replacing murine with human elements, the production of antibodies that neutralise the adalimumab injections is reduced.

Efficacy

Rheumatoid arthritis

TNF inhibitors are recommended for the treatment of severe and active rheumatoid arthritis after an adequate trial of disease modifying agents (DMARDs) has failed. International consensus guidelines recommend that therapy with two DMARDs in an adequate dosage for an adequate duration (unless not tolerated or contraindicated) should be trialled before TNF inhibitors are indicated.[5] TNF inhibitor therapy is expensive (about $18 000 per year), and the PBS authority listing requires the failure of four DMARDs, including methotrexate and three DMARDs used in combination, before therapy for rheumatoid arthritis will be reimbursed. The efficacy and safety of TNF inhibitors was initially demonstrated in rheumatoid arthritis trials where the TNF inhibitor was used as monotherapy; these were followed by combination studies with methotrexate and other disease modi-

1 Characteristics of licensed tumour necrosis factor (TNF) inhibitors

	Etanercept	Infliximab	Adalimumab
Class	Soluble TNF receptor	TNF-α monoclonal antibody	TNF-α monoclonal antibody
Construct	Recombinant fusion protein	Chimeric monoclonal antibody	Human monoclonal antibody
Origin	Entirely human	Human and murine	Entirely human
Half-life (days)	4.8	9.5	12–14
Use	Effective as monotherapy or in combination with methotrexate therapy	Effective in combination with methotrexate therapy (rheumatoid arthritis)	Effective as monotherapy, or in combination with methotrexate therapy (rheumatoid arthritis)
Dosage			
Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis	25 mg subcutaneously twice a week	3–5 mg/kg intravenously at 0, 2, and 6 weeks; then 4–8 weekly maintenance	40 mg subcutaneously fortnightly
Crohn's disease	Did not show benefit	5 mg/kg intravenously at 0, 2, and 6 weeks (fistulating); then 8 weekly maintenance	40 mg subcutaneously fortnightly under evaluation ◆

fying drugs in severe established disease.[6-10] Subsequent combination trials in patients with early disease showed complete remission rates up to 42% at 2 years of treatment, and prevention of the progression of bone erosion (a surrogate for prevention of irreversible joint damage that leads to deformity and disability) could be shown in 80%.[7] TNF inhibitors have proven efficacy as (i) monotherapy (E1; based on National Health and Medical Research Council levels of evidence[11]); (ii) in combination with methotrexate and with other DMARDs (E1); (iii) added to or replacing pre-existing therapy (E1); (iv) in patients who have not previously been treated with methotrexate (E1); and (v) as the first DMARD (E1). Significant improvements are seen in symptoms (especially reduced fatigue and increased energy), signs, function and quality of life.[6-10] Efficacy in juvenile chronic arthritis has also been shown.[12] There is no evidence of superiority of one agent over another (E3), and failure to respond to one agent does not preclude response to another (E3).

Psoriatic arthritis

No conventional DMARD therapy prevents progression of this disease as determined by radiological imaging. However, etanercept and infliximab have been shown to control rash, improve symptoms, quality of life and function, as well as to slow radiologically evident progression in this disease (E2).[13,14] Adalimumab has recently been shown to have similar efficacy.[15] PBS listing for this indication is awaited.

Ankylosing spondylitis

No conventional DMARD therapy has been shown to prevent or reduce radiologically evident progression of this disease. However, randomised controlled trials of etanercept and infliximab as monotherapy have shown their ability to retard radiologically evident progression and significantly reduce symptoms and improve quality of life and function (E2).[16-18]

Crohn's disease

In double-blind randomised placebo-controlled clinical trials, infliximab significantly decreased the Crohn's disease activity index in "treatment-resistant" inflammatory disease, and significantly reduced the number of draining fistulae in fistulating Crohn's disease.[19] Moreover, a study with infliximab is the only randomised placebo-controlled medical treatment trial to ever show improvement in fistulating Crohn's disease.[20] A clinical trial evaluating infliximab in long-term treatment showed it useful for maintaining remission in about 60% of patients with Crohn's disease (E2).[21] The therapy dramatically improves endoscopic disease manifestations, diarrhoeal symptoms and wellbeing. There are promising emerging data for other monoclonal anti-TNF-α therapies, including the pegylated human CDP870 monoclonal antibody[22] and the completely human adalimumab, in the treatment of Crohn's disease,[23] but these drugs are not licensed for this indication at present. The recently completed Active Ulcerative Colitis Trial 1 (ACT 1) shows a significant benefit for infliximab in treating severe chronic ulcerative colitis where patients were also taking conventional thiopurine immunosuppression and/or steroids.[24] Safety was a significant issue, with opportunist infection causing one death and an association with three cancers in the active treatment arms.[25]

Many of the "treatment-resistant" cases of Crohn's disease reported in the original and subsequent manufacturer-sponsored trials were in patients treated with steroids, but who had not been treated with thiopurine immunosuppression. Such cases would not be termed treatment-resistant in accepted Australian practice where immunosuppression is the normal medical treatment standard. However, the first available biological treatment, infliximab, has certainly transformed the treatment of difficult cases of Crohn's disease. Our review of the early Australian experience with infliximab in Crohn's disease suggests that it has a significant clinical role as an acute adjunctive therapy with conventional thiopurine immunosuppression.[26] This is supported by other more recent retrospective studies.[27,28] There has not been a formal, well designed randomised controlled trial of combination TNF inhibitor and conventional immunosuppression in Crohn's disease. This contrasts with rheumatoid arthritis and ulcerative colitis,[24] where trials have either had concomitant conventional immunosuppressive therapy as an inclusion criterion, or stratified patients with treatment-resistant disease who had already been stabilised on conventional immunosuppression. In rheumatoid arthritis in particular, conventional immuno-

2 Major adverse effects of tumour necrosis factor inhibitors

- Injection site and infusion reactions
- Infection — opportunists including fungi and tuberculosis
- Lymphoproliferative disease — non-Hodgkins and Hodgkins lymphoma
- Demyelinating disease — reactivation of multiple sclerosis and optic neuritis
- SLE-like syndromes
- Aggravation of congestive cardiac failure

SLE = systemic lupus erythematosus. ◆

suppression is additive in its effect, both in terms of efficacy and suppressing antibodies to infliximab.[10]

Adverse effects

TNF inhibitors are generally well tolerated, with prompt onset of action and much earlier relief of symptoms compared with standard DMARD therapy in rheumatoid arthritis, or with standard immunosuppressive therapy in Crohn's disease. Box 2 lists the major adverse effects. Injection site reactions or intravenous infusion reactions of mild to moderate severity occur, and are managed with antihistamines, injection of hydrocortisone or, less commonly, cessation of therapy (E2).[6-10] Serious infections can occur including septic arthritis, infected prostheses and a variety of opportunist infections such as pneumocystis and tuberculosis (E2).[29] In particular, susceptibility to infection and reactivation of latent tuberculosis early after commencement of anti-TNF therapy, and dissemination in a miliary fashion has been documented (E2).[30] This means that patients commencing anti-TNF therapy should have a screening chest x-ray and Mantoux test. However, this guideline was developed primarily for the US and European populations. The interpretation of the Mantoux test in the Australian population, where previous BCG has been common and the prevalence of tuberculosis is low, is difficult. Induration of more than 10 mm and erythema of 15 or greater at 48–72 hours are considered appropriate to avoid clinically irrelevant positive results. Isoniazid therapy for 9 months is indicated if anti-TNF therapy is deemed necessary and the Mantoux result is significantly positive.[24,31] Demyelinating disorders such as reactivation of multiple sclerosis or optic neuritis have been reported.[32] The incidence of lymphoproliferative disease is increased in rheumatoid arthritis, especially in patients with high disease activity, but this also occurs in such patients on methotrexate therapy.[33,34] The TNF inhibitors may increase that risk (E3). Long-term controlled and adequately powered follow-up studies are required to settle this issue. There is no evidence that TNF inhibitors increase the incidence of other malignancies or recurrence in patients with prior malignancy in the controlled clinical trial database, but further observation in controlled and adequately powered studies are required (E3).[32] The development of antinuclear antibodies and dsDNA antibodies is not uncommon, but SLE (systemic lupus erythematosus)-like syndromes are much rarer and abate with drug cessation (E3-2).[32] Other rare reports include pancytopenia, aplastic anaemia,[32] and aggravation of congestive cardiac failure.[32] Safety, apart from anecdotal reports, is unknown in patients with hepatitis B and C infection, and data are limited in pregnancy or lactation.

3 Situations in which anti-tumour necrosis factor therapy is considered inappropriate for safety reasons[32]

- After previous tuberculosis (except after a full course of modern anti-tuberculosis therapy, ongoing isoniazid cover and the patient being made aware of the risks and benefits)
- Within 12 months of septic arthritis
- Patients with an infected prosthesis
- Patients with recurrent chest infections or bronchiectasis
- Patients with indwelling urinary catheters
- Patients with multiple sclerosis or demyelinating illness
- Within 10 years of any malignancy (apart from fully resected basal cell carcinoma more than 5 years before)
- During pregnancy and lactation
- Patients with congestive cardiac failure
- Patients with chronic cutaneous ulceration, but not pyoderma gangrenosum ◆

4 Important messages for patients

- Tumour necrosis factor (TNF) inhibitors offer major therapeutic gain, which can revolutionise quality of life and stop damage in selected patients
- These drugs are very expensive
- Side effects are rare, but can be serious (eg, decreased immunity to infections)
- When and how to use these drugs, and with what other medications, is under active study
- The long-term safety of TNF inhibitors is being evaluated ◆

Box 3 describes situations in which TNF inhibitors are not appropriate.

Conclusion

The TNF inhibitors represent an important new group of agents shown to significantly improve symptoms and signs, function and quality of life, induce remission and reduce objectively measured damage in patients with chronic inflammatory and rheumatic conditions.

In rheumatoid arthritis, there is Level 1[11] evidence for their use as subcutaneous or intravenous injections, generally in combination with methotrexate therapy.

In Crohn's disease, there is accumulating Level 3[11] evidence for their use with conventional immunosuppressive agents. Prospective studies using these drugs in combination therapy are awaited. The results of these studies will be important to ensure rational use of these expensive new therapies.

Toxicity includes injection and infusion reactions, infection risk (particularly with tuberculosis reactivation), and SLE-like syndromes. Risk of lymphoproliferative and demyelinating disease are under ongoing assessment in long-term follow-up studies.

Box 4 contains important messages for patients.

Competing interests

PN has received research grants for clinical trials and has lectured on behalf of, or consulted for, Wyeth, Abbott and Schering-Plough. TF is involved with clinical trials and has served on an industry advisory board for Schering-Plough.

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