Clinical use of anti-TNF-α biological agents

A guide for GPs

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BACKGROUND
Tumour necrosis factor-α (TNF-α) inhibitors are a new class of injectable drugs, under the umbrella term 'biological agents', now available for the treatment of rheumatoid arthritis and other chronic inflammatory conditions including juvenile idiopathic arthritis, Crohn disease, psoriasis and psoriatic arthritis.

OBJECTIVE
The aim of this review is to provide an overview of TNF-α inhibitors and highlight the key practical issues of relevance to general practitioners.

DISCUSSION
TNF-α inhibitors may have a potent effect in reducing inflammation and possibly inducing remission where conventional disease modifying drugs have failed to do so. These drugs are associated with an increased risk of infection as well as other potentially serious side effects. Their use is restricted to the relevant specialist prescribing the drug and are only available on the Pharmaceutical Benefits Scheme under strict prescribing criteria. The role of the GP is critical in identifying patients suitable for referral to consider commencing treatment and in monitoring patients on long term therapy.

Tumour necrosis factor-α (TNF-α) is a pro-inflammatory cytokine known to have a critical role in the pathogenesis of various inflammatory or immune mediated diseases such as rheumatoid arthritis (RA) and ankylosing spondylitis. TNF-α inhibitors are biological agents that specifically target key these inflammatory mediators. This class of drug is now in relatively common clinical use in Australia.

Current clinical use in Australia

There are three TNF-α inhibitors available for clinical use in Australia (*Table 1*):

- infliximab (Remicade®)
- adalimumab (Humira®), and
- etanercept (Enbrel®).

All three agents block the biologic effects of TNF-α, although there are some differences in their structure, pharmacokinetics and mechanisms of action. Both infliximab and adalimumab are anti-TNF-α monoclonal antibodies that bind specifically to human TNF-α with high affinity and neutralise the biological activity of TNF-α by inhibiting its binding to its receptors.[1] They do not bind TNF-β. The main difference between these two agents is that infliximab is a chimeric monoclonal antibody, composed of both human and murine proteins and given as an intravenous infusion; while adalimumab is entirely of human origin given as subcutaneous injections every 2 weeks. Methotrexate can be co-administered with infliximab to prevent the development of neutralising antibodies to infliximab that could reduce its therapeutic efficacy. Adalimumab, containing only human proteins, does not have this potential problem.

Etanercept is not a monoclonal antibody but a fusion protein that acts as a 'decoy receptor' for TNF-α and acts competitively to inhibit the binding of TNF to its cell surface receptor. Etanercept is administered as a subcutaneous injection 1–2 times per week, and binds to both TNF-α (primarily to its soluble form) and in addition TNF-β, rendering them biologically inactive by inhibiting their interaction with cell surface TNF receptors.[1,2]

The efficacy and safety profile of the TNF-α blockers can be considered, in general, as a class effect; although some differences may exist between the three agents.[2]

When are TNF-α blockers indicated?

TNF-α blockers have demonstrated efficacy in large, randomised controlled clinical trials either as monotherapy or in combination with other anti-inflammatory or disease

Table 1. TNF-α inhibitors available for clinical use in Australia

Infliximab (Remicade®)	Adalimumab (Humira®)	Etanercept (Enbrel®)
Monoclonal antibody (mAb) against TNF-α	mAb against TNF-α	Soluble decoy receptor for TNF-α
Human and mouse proteins	Entirely human proteins	Entirely human fusion protein
Intravenous infusion	Subcutaneous injection	Subcutaneous injection
Baseline infusion followed by variable infusions at 2–8 weekly intervals	Injections every 2 weeks	Administration 1–2 times per week

Table 2. PBS approved clinical indications for the use of TNF-α blockers in Australia

Rheumatologic indications
Severe and active RA, refractory to an adequate trial of disease modifying antirheumatic drugs (DMARDs)
Active polyarticular juvenile idiopathic arthritis (JIA), refractory to one or more DMARDs
Ankylosing spondylitis
Psoriatic arthritis
Gastrointestinal indications
Moderate to severe Crohn disease (including fistulating Crohn disease) with inadequate response to conventional therapies (TGA approved but not yet PBS listed)
Dermatological indications
Moderate to severe psoriasis

modifying antirheumatic drugs (DMARDs) in the treatment of chronic inflammatory diseases (*Table 2*). They appear to be among the most effective treatments available for adult RA, juvenile idiopathic arthritis, ankylosing spondylitis and Crohn disease (with some differences between agents).[2,3]

In addition, as of August 2006, TNF-α inhibitors have been Pharmaceutical Benefits Scheme (PBS) listed for use in psoriatic arthritis (dramatic effects on psoriatic skin disease have also been noted).[4] Other clinical indications are anticipated as studies investigate the usefulness of these agents in the treatment of other inflammatory diseases.

TNF-α inhibitors can induce disease remission and prevent both clinical and radiological disease progression in rheumatologic diseases, with significant improvement in patient symptoms, function and quality of life.[3] This represents a significant advancement in the treatment of inflammatory joint diseases, as no previous DMARDs have been able to achieve such marked and dramatic clinical effects or prevent joint destruction.

Treatment with anti-TNF-α blockers can only be initiated and continued by an appropriate specialist (rheumatologist, gastroenterologist, dermatologist or clinical immunologist, via PBS authority application). Despite the significant efficacy of TNF-α blockers, their use under the PBS is restricted to a subset of patients with severe and progressive disease poorly responsive to conventional therapies, mainly due to the high costs associated with these biological agents. For example, patients with RA must meet the following criteria before TNF-α blockers can be used under the PBS:

- failure to respond to an adequate trial of at least three DMARDs, including methotrexate, for a minimum of 3 months
- clinical evidence of active disease, ie. multiple, actively inflamed joints, and
- persistently elevated inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]).

It is also important to note that not all patients respond to TNF-α inhibitors, the reasons for which are currently unclear, therefore patients should be informed of this before commencement of therapy and monitored carefully for a therapeutic effect. There is no clear evidence to support superiority of one anti-TNF-α blocker over another in rheumatic disease and failure to respond to one agent does not preclude response to another.[3,5] However, in Crohn disease, infliximab has been shown to be of clear benefit, with adalimumab also having some efficacy; however etanercept does not have significant demonstrated benefit.[5]

Comanagement with specialists

Unfortunately, TNF-α blockers have not been shown to induce long term drug free disease remission, therefore there will be an increasing number of patients with rheumatologic and other inflammatory diseases being treated with an anti-TNF-α agent long term. General practitioners play an important role in the comanagement of such patients, including the recognition and timely referral of candidate patients who may benefit from a TNF-α blockade, and also being aware of and monitoring for, potential treatment related adverse effects.

Pretreatment considerations

Although TNF-α blockers are generally well tolerated, the existence of any contraindications to the use of these agents (*Table 3*) needs to be considered before the commencement of therapy.[2] Re-activation of latent tuberculosis (TB) infection has been reported with the initiation of anti-TNF-α treatment; appropriate screening of patients with Mantoux test and chest X-ray should be performed before starting therapy (see *Case study 1*).[2,3] It is worth noting that Mantoux testing can give false negative results due to anergy in an immunosuppressed patient. A new test, the QuantiFERON-TB Gold assay is available as an alternative or adjunct for the diagnosis of latent TB.[6] This assay depends on the detection of interferon-α after whole blood is incubated with *Mycobacterium tuberculosis* specific antigens. It also has the advantage of having a positive control. Active or latent TB must be treated with a standard anti-TB

Table 3. Contraindications for the use of TNF-α blockers

Absolute
Active infections (including infected prosthesis, severe sepsis)
History of recurrent or chronic infections (eg. bronchiectasis)
After previous, untreated TB
Moderate to severe congestive cardiac failure
Multiple sclerosis or optic neuritis
Combination treatment with anakinra (IL-1 receptor antagonist).
Active or recent history (past 10 years) of malignancy except for skin cancer
Relative
Pregnancy
Lactation
HIV, hepatitis B, hepatitis C infection

Case study 1 – treatment of latent TB

Mrs B, 55 years of age, has severe RA and meets the PBS criteria for treatment with etanercept. Her history reveals that she grew up in Southeast Asia before migrating to Australia. A chest X-ray does not show any abnormalities, but a Mantoux test is positive at 32 mm. She was referred to a hospital chest clinic where she was commenced on isoniazid therapy to prevent reactivation of latent TB. Isoniazid was used for 3 months before starting etanercept which will be continued for a total of 9 months.

Case study 2 – use of anti-TNF drugs in the perioperative period

Mrs M, 60 years of age, has severe RA and is on therapy with adalimumab, methotrexate and prednisolone. She is due to have cataract extraction and intraocular lens implants. She consults her GP and rheumatologist preoperatively and is advised to continue her regular medications without change. The surgery and recovery go smoothly.

Six months later Mrs M needs to have a total hip replacement. This time she is advised to omit the dose of adalimumab before surgery to decrease the risk of infection of the prosthesis. Postoperatively there is some erythema around the wound at day 5. There is no sign of flare up of her RA. She is treated with antibiotics for potential cellulitis and another dose of adalimumab is omitted. In order to avoid the potentially serious problem of infection of her prosthesis, Mrs M's doctors ensure the wound is well healed and that there is no sign of infection before injections are recommenced.

regimen in consultation with a respiratory or infectious diseases physician.

Monitoring during therapy

All clinicians involved in the care of patients being treated with TNF-α blockers should be aware of potential treatment related adverse effects and monitor patients accordingly (*Table 4*).[3,7,8]

The most important adverse effect of anti-TNF-α therapy is the increased risk of severe infections, which results from the blockade of a critical pro-inflammatory cytokine in patients already on other anti-inflammatory or immunosuppressive agents. The different half lives of the various anti-TNF-α agents become relevant. Adalimumab which has the longest half life (2 weeks) of the three agents, produces a longer period of immunosuppression and risk of infection per dose, compared to, for example, etanercept, which has a much shorter half life of about 5 days. Particular caution should be used in patients already at increased risk of infections such as those with diabetes.

General practitioners should play an important role in educating their patients regarding the possible side effects of anti-TNF-α therapy and highlight some of the early warning symptoms. Patients should be instructed regarding the rudiments of differentiating simple viral illnesses and minor infections from those with the potential to cause serious harm, and should be instructed to inform their GP or TNF-α inhibitor prescriber when signs of the more serious infections occur.[3] Obviously the GP will have a lower threshold for initiating antibiotic therapy in patients on a TNF-α blocker. In patients who develop serious infections, the TNF-α blocker should be ceased, at least until the complete resolution of the infection, in consultation with the specialist primarily managing the anti-TNF-α therapy.

Special precautions to minimise the risk of infection should be taken in the pre- and post-operative periods in patients undergoing routine elective or emergency surgery, particularly where prosthetic implants are involved (see *Case study 2*). These guidelines are empirical, but as a general guide, if surgery involves possible sepsis, such as abdominal surgery, it would be best to omit the anti-TNF-α therapy until the patient shows postoperative healing. In the case of elective surgery, omitting a dose of treatment preoperatively may lessen the risk of infection.

The most common side effects of this class of medication are:

- injection site reactions to subcutaneously administered drugs, or
- infusion reactions with infiximab (*Table 4*).

The cutaneous injection site reaction consists of local erythema and swelling which usually subsides within 24 hours. It can be lessened by predosing with an antihistamine and does not interfere with the efficacy of the drug, nor does it necessitate stopping treatment. Infusion reactions can also be treated by premedication, which will usually be arranged by the hospital centre administering the infusion.

The clinical response of the inflammatory disease to the TNF-α blockers will be primarily monitored by the rheumatologist (or other relevant specialist). This involves

Table 4. Treatment related adverse effects of TNF-α blockers

Relatively common
Injection site reaction (mild redness or itch lasting a few days)
Intravenous infusion reactions (fever, chills, nausea)
Development of antibodies against the TNF-α blocker*
Development of antinuclear antibodies and anti-DNA antibodies
Uncommon to rare, but serious
Severe infection/sepsis (eg. septic arthritis, infected prosthesis, acute abscess)
Reactivation of latent TB or progression of recently acquired TB
Opportunistic infections, particularly fungal (eg. histoplasmosis or coccidioidomycosis)
Drug induced systemic lupus erythematosus (SLE)
Exacerbation of congestive cardiac failure
New onset or exacerbation of CNS demyelinating disorders (eg. multiple sclerosis, optic neuritis and Guillain-Barre syndrome)
Possible increased risk of malignancy, in particular, lymphoma**

* The chimeric monoclonal antibody, infliximab, is the most immunogenic of the TNF-α blockers and is associated with the highest incidence of human antichimera antibody formation

** There is controversy over the increased risk of lymphoma with some authors finding the risk of lymphoma is not increased over the background of patients with longstanding RA,[9] while others find that the overall risk of malignancy is increased[10]

monitoring the level of inflammatory activity and disease progression. For example in RA, by monitoring:

- the number of joints that are inflamed
- the inflammatory markers (ESR and CRP)
- requirements for other anti-inflammatory agents, and
- functional improvements.

TNF-α blockers appear to have a more rapid onset of clinical effect than conventional DMARDs and, in general, clinical improvement should be seen within 4–12 weeks.[3]

Vaccinations, other than live attenuated vaccines (as for other immunosuppressed patients), may be given to patients receiving TNF-α blockers.[2] There are potential theoretical reasons that vaccinations against pneumonia and influenza may be less effective in patients on TNF blocking agents and these vaccinations should be given, if possible, before commencing the use of these agents.[3]

Conclusion

TNF-α blockers represent a new class of biological DMARDs that have revolutionalised our clinical management of chronic debilitating inflammatory diseases such as RA and ankylosing spondylitis. General practitioners and others involved in the care of such patients need to be aware of the potential efficacy and risks of treatment with these agents. Due to the need for continued treatment with these agents to maintain disease remission, all physicians need to make long term observations for efficacy and toxicity in a collaborative manner, and appropriately provide information to patients regarding the potential benefits and risks of therapy.

Resource

American College of Rheumatology. Update on safety issues concerning TNF inhibitors and information for patients. Available at: www.rheumatology.org/publications/hotline/0506JAMATNF.asp.

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