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# TNF inhibitors: an update

## Tumour necrosis factor

Tumour necrosis factor (TNF) is an inflammatory cytokine involved in the pathogenesis of a number of inflammatory or immune mediated conditions.

## TNF inhibitors available in New Zealand

Adalimumab (Humira) and infliximab (Remicade) are both monoclonal antibodies active against TNF. They neutralise the inflammatory effect of TNF by binding to it and inhibiting binding with its target receptor.

Adalimumab contains only human proteins and is administered by subcutaneous injection, usually every two weeks. Infliximab contains both human and mouse proteins and is administered by intravenous infusion every eight weeks.<sup>1</sup>

Etanercept (Enbrel) is a genetically engineered human soluble TNF receptor that works by binding to TNF and blocking its activity.<sup>2</sup> It is given by subcutaneous injection twice weekly.

## Place in therapy

TNF inhibitors are used in the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, severe psoriasis, Crohn's disease and juvenile idiopathic arthritis when there is high disease activity despite a full trial of conventional therapies.

## Contraindications to TNF inhibitor use

TNF inhibitors are not suitable for people who have :<sup>1</sup>

- Severe active infections (e.g. infected prosthesis, severe sepsis)
- Untreated active or latent tuberculosis
- Moderate to severe congestive heart failure
- Multiple sclerosis or optic neuritis

## Adverse effects

### Common adverse effects

The most common adverse effect with TNF inhibitors injected subcutaneously is **injection site reactions**. Injection site reactions can be lessened with pre-treatment antihistamines or treated with local application of ice or topical corticosteroid unless infection is present on the skin.

**Infusion reactions** may occur with infliximab. They can often be prevented by premedication with a sedating antihistamine and paracetamol.<sup>4</sup>

### Rare but serious adverse effects

**Reactivation of tuberculosis (TB)** is most likely to occur in the first 12 months of treatment therefore extra vigilance is required during this time. British guidelines suggest screening all patients for TB prior to commencing treatment with a TNF inhibitor.<sup>5</sup> This includes taking a history to check for any prior TB infection or treatment and performing a clinical examination and a chest x-ray. Patients who are found to have latent or active TB should be treated prior to commencing a TNF inhibitor.

## Adalimumab funded for more indications

In addition to being subsidised for the treatment of severe rheumatoid arthritis, access to subsidised adalimumab (Humira) has recently become widened to include last-line treatment of ankylosing spondylitis, Crohn's disease, severe chronic plaque psoriasis and psoriatic arthritis. Funding for all subsidised indications is subject to Special Authority criteria being met.

Adalimumab has been shown to:<sup>3</sup>

- Reduce signs and symptoms of ankylosing spondylitis, psoriatic arthritis and rheumatoid arthritis
- Inhibit progression of structural damage in rheumatoid and psoriatic arthritis
- Reduce signs and symptoms and maintain clinical remission in Crohn's disease
- Decrease epidermal thickness and inflammatory infiltration in plaque psoriasis

**Note:** Etanercept is still funded, subject to Special Authority criteria, for juvenile idiopathic arthritis and infliximab will still be available for treatment in hospital (if funded by the hospital).

## Monoclonal antibody naming conventions

Generic drug names are intended to make drugs identifiable and to avoid confusion with other drug names. All monoclonal antibodies are recognisable from their suffix stem of -mab (e.g. infliximab, adalimumab). They also have a specific sub stem that reflects the species origin of the antibody:<sup>2</sup>

Sub-stem	Origin of antibody	Example
-o-	Mouse	No examples in New Zealand
-xi-	Chimeric (e.g. mouse + human)	Infliximab
-zu-	Humanised	Palivizumab
-u-	Human	Adalimumab



Patients who qualify for TNF inhibitor therapy in New Zealand have usually trialled multiple DMARDs previously. Tuberculin skin tests (Mantoux test) are significantly affected by immunosuppressive therapy therefore their value in this setting is questionable.<sup>6</sup>

### Serious opportunistic infections

TNF inhibitors should not be initiated in the presence of serious infections and extreme caution should be used in patients with increased risk of infection, e.g., bronchiectasis, history of chronic leg ulcers and history of septic arthritis.

Infection developing in patients on TNF inhibitors can quickly become severe and lead to life-threatening or fatal sepsis.

 **Best practice tip:** In patients taking TNF inhibitors it is important to treat any infections early, even if minor,<sup>7</sup> Patients should be advised of the increased risk of infection and the need to consult their GP if signs of infection occur.

Therapy should be discontinued if a serious infection develops but can be restarted once it has completely resolved.

To minimise the risk of infection in patients who are undergoing major surgery, TNF inhibitor therapy should be withheld for two to four weeks prior to surgery and can be resumed post-operatively if there are no signs of infection and wound healing is sufficient.<sup>5</sup>

### Malignancy, heart failure and demyelinating disease are other potential adverse effects

Malignancies, including lymphoma, have been reported in association with TNF inhibitors however the risk does not seem to be elevated above the risk of malignancy associated with rheumatoid arthritis. Caution should be exercised in patients with current or recent malignancy. Until there is conclusive evidence of safety it would be advisable to avoid TNF inhibitors in patients with a history of lymphoma.

TNF inhibitors may be associated with congestive heart failure. They are contraindicated in moderate to severe heart failure (NYHA class III/IV) and should be discontinued if heart failure develops or worsens.<sup>5</sup>

Demyelinating disease has been associated with TNF inhibitor use. Symptoms of demyelination include confusion, ataxia and changes in sensation. TNF inhibitor therapy should be discontinued in patients who develop symptoms of demyelination and are best avoided in people who have conditions associated with demyelination such as multiple sclerosis.<sup>4</sup>

### Drug induced lupus erythematosus

See Research Snippets (page 48) for further information.

### Monitoring

Monitoring may vary depending on whether other DMARDs are used in conjunction with TNF inhibitors but as a guide test the following at baseline, then monthly for six months and then every three to six months thereafter:

- Complete blood count - stop therapy and seek advice for WBC < 3.5 x 10<sup>9</sup>/L, neutrophils < 2 x 10<sup>9</sup>/L, platelets < 150 x 10<sup>9</sup>/L
- Liver function tests - seek advice if ALT level greater than twice the upper limit of normal<sup>8</sup>

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