



Tumour necrosis factor inhibitors

What do they do?

Tumour necrosis factor (TNF) alpha, an inflammatory cytokine, is involved in the pathogenesis of rheumatoid arthritis.¹ The three TNF inhibitors available in New Zealand (adalimumab, etanercept and infliximab) target this cytokine and block its effect. These parenteral agents are given by either self administered subcutaneous injection (adalimumab once a fortnight, etanercept weekly) or hospital administered intravenous infusion (infliximab every two months after induction).

What is their place in therapy?

In New Zealand TNF inhibitors are mainly used in individuals with rheumatoid arthritis which remains active despite optimal disease modifying anti-rheumatic drugs (DMARDs). Cochrane reviews have concluded that TNF inhibitors significantly reduce disease activity in rheumatoid arthritis compared to placebo.^{2,3,4}

All three drugs are registered for use in rheumatoid arthritis, but only adalimumab is funded on special authority for this indication (see box below). Etanercept is funded on special authority for juvenile idiopathic arthritis. Patients who fail to respond to one TNF inhibitor, or who discontinue its use because of adverse effects, may respond to a second TNF inhibitor.³

Adalimumab for rheumatoid arthritis – Pharmac criteria

Patients must have severe erosive rheumatoid arthritis that has not responded to a three month trial of each of the following; methotrexate, combination (triple) therapy, leflunomide or cyclosporin. They must also meet disease activity criteria (e.g. at least 20 joints affected). To continue to receive subsidy for

adalimumab patients must also show a 50% decrease in active joint count and a clinically significant response after four months of treatment.

For full details of special authority criteria see: www.pharmac.govt.nz/2008/10/01/SA0812.pdf

Safety concerns

The most common adverse effect with TNF inhibitors is injection site reactions. Reactions can be treated with the local application of ice or corticosteroid cream unless complicated by infection.⁵

Other more serious safety concerns are:

- Reactivation of tuberculosis (TB) – most likely 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. Patients who are found to have latent or active TB should be treated.
- Congestive heart failure – Infliximab has been associated with an increase in mortality and hospitalisation due to cardiac failure. TNF inhibitors should not be started in people with Grade 3 or 4 congestive heart failure and used with caution in Grade 1 and 2. All patients on TNF inhibitors should be monitored for signs and symptoms of cardiac failure.⁶
- 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. Patients should be advised of the increased risk of infection. Therapy should be discontinued if a serious infection develops but can be restarted once the infection has completely resolved.

Other contraindications to TNF inhibitors include a history of demyelinating disease, pregnancy and breastfeeding.⁶

Live vaccines should not be administered to individuals receiving TNF inhibitors.

Monitoring

No specific laboratory monitoring is required during TNF inhibitor therapy as haematological and liver test abnormalities are rarely caused by these agents. Most individuals will require ongoing laboratory monitoring for concomitant DMARD therapy (see Table 1, over page, for details on DMARD monitoring).

References:

1. Australian Medicines Handbook 2006.
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3. Blumenauer B, Judd M, Wells G, et al. Infliximab for the treatment of rheumatoid arthritis. *Cochrane Database Syst Rev* 2002; 3: CD003785.
4. Blumenauer B, Judd M, Cranney A, et al. Etanercept for the treatment of rheumatoid arthritis. *Cochrane Database Syst Rev* 2003; 4: CD004525.
5. Jones P. Medical management of rheumatoid arthritis. *N Z Fam Physician* 2007; 34(6): 427-31.
6. Ledingham J, Deighton C. Update on the British Society for Rheumatology guidelines for prescribing TNF α blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). *Rheumatology* 2005; 44(2): 157-63.

