



## TNF inhibitors for inflammatory arthritis in New Zealand

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### Abstract

For the vast majority of the estimated 100,000 New Zealanders who suffer from rheumatoid arthritis (RA),<sup>1</sup> relatively inexpensive disease-modifying antirheumatic drugs (DMARD) regimens are sufficient to control inflammatory disease and maintain long-term function. Some DMARDs have been shown to slow, but not arrest, the progression of erosions.<sup>2</sup> All but a few of those who suffer from ankylosing spondylitis (AS) can manage full social participation with non-steroidal anti-inflammatory drugs (NSAIDs) and an exercise regimen. For the small subset of arthritis sufferers who have disabling pain and progressive damage from uncontrolled inflammatory disease, the advent of the biological era offered great promise. In most of the developed world, this promise is being delivered to patients with an expanding range of diseases including RA, AS, and psoriatic arthritis, but central government (PHARMAC) funding for TNF inhibitors in New Zealand has until recently been limited to etanercept for approximately 40 patients with juvenile inflammatory arthritis.

### TNF inhibitors

Increased understanding of the immunopathogenesis of inflammatory joint disease has recognised tumour necrosis factor (TNF) as a central cytokine promoting inflammation.<sup>3</sup> In humans, TNF antagonists have been shown to control disease activity in early and established RA, AS, and psoriatic arthritis. There are currently three TNF antagonists licensed for use in New Zealand (infliximab, etanercept, and adalimumab) available at a cost of NZ\$20,000 to NZ\$30,000 per patient per annum.

### Infliximab

Infliximab (Remicade<sup>®</sup>) is a chimeric IgG1 anti-TNF antibody containing the antigen-binding region of the mouse antibody and the constant region of the human antibody. Infliximab combined with methotrexate has been shown to improve disease control in over half of patients with RA failing methotrexate monotherapy, and to arrest the progression of erosions over 12 months of treatment regardless of the clinical response.<sup>4</sup>

In AS, infliximab reduced activity of spinal inflammatory disease by at least 50% in 50% of patients with severe active disease, with onset of improvement within 2 weeks.<sup>5</sup> This benefit was sustained over a 2-year treatment period.<sup>6</sup> Infliximab is given by intravenous infusion: initially 3 infusions over 6 weeks, then at 8-week intervals, with a dose of 3 mg/kg in RA and 5 mg/kg in AS.

### Etanercept

Etanercept (Enbrel<sup>®</sup>) is a soluble TNF-receptor fused to the Fc portion of IgG that binds to TNF, preventing interaction with its receptor. Etanercept, at a dose of 25 mg

subcutaneously twice weekly, reduces arthritis activity in patients with early<sup>7</sup> and established RA.<sup>8</sup> In AS, etanercept rapidly reduced both axial and peripheral joint disease;<sup>9</sup> and in psoriatic arthritis, etanercept reduces peripheral arthritis and improves psoriasis.<sup>10</sup>

## **Adalimumab**

Adalimumab (Humira<sup>®</sup>) is a recombinant human IgG1 monoclonal antibody that binds to human TNF impairing cytokine binding to its receptors and lysing cells that express TNF on their surface. In patients with active RA despite therapy with optimum doses of methotrexate, addition of adalimumab rapidly reduces disease activity.<sup>11</sup> Adalimumab is administered subcutaneously every other week.

## **Adverse events and contraindications**

In clinical trials, all TNF inhibitors have been well tolerated. Etanercept and adalimumab occasionally cause injection site reactions which decline over time and are uncommon after 2 months of use.<sup>12</sup> Infliximab infusion can cause fever, nausea, and rash in up to 20% of patients, which is usually controlled with premedication.<sup>13</sup> TNF inhibition has been associated with the development of serious infectious diseases, both with common Gram-positive and Gram-negative bacteria and opportunistic organisms such as *Mycobacterium tuberculosis*, *Cryptococcus*, and *Aspergillus*.<sup>14</sup> There is a significant increased risk of reactivation of latent mycobacterial infection (particularly with infliximab),<sup>15</sup> and all patients are screened for latent tuberculosis before treatment. There are rare reports of demyelinating neurological disease, pancytopenia, and drug-induced lupus occurring during use of TNF inhibitors.<sup>12</sup> TNF inhibition worsens congestive heart failure and there use should be avoided in patients with class II, III, or IV congestive heart failure. There have been no studies of safety during pregnancy and therefore adequate contraception should be used.

## **TNF inhibitors and PHARMAC**

The Pharmaceutical Therapeutic Advisory Committee (PTAC) first considered funding etanercept in August 2002. It recommended that etanercept be given moderate priority for adult rheumatoid arthritis, which was regarded as a high cost, high benefit situation, and high priority for juvenile inflammatory arthritis, which they regarded as a high cost, very high benefit situation involving many fewer patients.

Etanercept has been funded for juvenile arthritis since February 2004, but up to now PHARMAC has not funded TNF inhibitors for adult inflammatory arthritis. This is out of step with countries such as the United Kingdom, Europe, USA, and Australia where, over the last 7 years, all three TNF inhibitors have become funded for use in RA, AS, and psoriatic arthritis in children and adults.

There is considerably more scientific evidence in to support the use of etanercept in adult RA than in childhood arthritis. The initial PTAC recommendation for adult RA appears to have been based on projected costs rather than science. A complaint to the Human Rights Commission that this policy discriminates on the basis of age has recently been given a favourable hearing.

In February 2005, PHARMAC published a Hospital Pharmaceutical Assessment Summary Discussion Document on infliximab and etanercept for RA.<sup>16</sup> In PHARMAC's view, these drugs are not cost-effective and fail to achieve an acceptable cost per QALY. Deficiencies in the methodologies used to reach this conclusion have been highlighted by local and international commentators. Quite apart from the fact that the RCT-based QALY calculations are invalidated in clinical practice by entry and exit criteria that define a high-need high-response target group, the long-term benefit of erosion reduction is completely overlooked by basing calculations on the surrogate outcome measure of short-term changes in function. It is particularly inappropriate to use methotrexate as a comparator given that the proposed criteria include failure of methotrexate therapy as a prerequisite. Nevertheless, the document has been circulated to DHBs and, whether intended or not, has served as a barrier to DHB funding of TNF inhibitors.

Cost-benefit analyses based on randomised control trials will inevitably underestimate the social and economic gains provided by successful therapy. It has recently been reported that the cost of arthritis to the New Zealand economy for 2005 will be NZ\$2.35 billion, of which only one-quarter are health sector costs.<sup>1</sup> For the patients who meet the proposed criteria for funding of a TNF inhibitor, the non-health sector costs are likely to be proportionately even higher. It seems obvious that targeting this group with therapy that restores function and arrests joint damage will reap economic rewards down the line.

In the last few days, PHARMAC has announced a proposal to list adalimumab on the pharmaceutical schedule. The prospect of TNF inhibitors for adult RA is greatly welcomed by local rheumatologists and arthritis patients, but delays in funding have caused considerable harm, and will continue to do so for New Zealand patients with severe psoriatic arthritis and ankylosing spondylitis for whom the prospect of relief in the next 2 years is unlikely, based on the experience with RA.

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