Research Review
PRODUCT REVIEW

Etanercept (Enbrel®)

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This review discusses the evidence in support of the use of etanercept (Enbrel®) in the treatment of patients with inflammatory arthritis including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile idiopathic arthritis. These are all painful and often debilitating conditions that can create a massive burden of disease for the individual and society as a whole. While many patients find the traditional DMARD regimens are sufficient to control their disease, a significant percentage of them do not respond and require an alternative therapeutic strategy.

Etanercept is one of a group of "biologic agents" that not only reduce the clinical signs of disease but also prevent the progressive destruction of joints. Until recently, government funding for these drugs was limited to adalimumab for adult inflammatory arthritis and etanercept for JIA. The recent decision by PHARMAC to widen the access for etanercept to include adults has given New Zealanders a degree of choice which has been available to patients overseas for a number of years.

Incidence and prevalence of arthritis in New Zealand

In the absence of detailed New Zealand epidemiological studies, the best estimate of community arthritis prevalence obtainable is from well-designed self-report surveys. The Ministry of Health's New Zealand Health Survey (NZHS) provides such data. The most recent NZHS was conducted between August 2002 and September 2003 and had over 12,000 respondents including 3,990 Māori, 790 Pacific peoples and 940 Asian people. According to this survey, arthritis including rheumatoid arthritis (RA), osteoarthritis or other type of arthritis (e.g. gout) affects 1 in 6 New Zealanders over the age of 15, estimated to be over half a million New Zealanders. With an ageing population, this is predicted to rise to nearly 1 in 5 New Zealanders by 2020; prevalence is expected to grow to around 719,300 people by then (19.2% of the population aged 15 or over), approaching 1 in 5 people, largely due to demographic ageing. Approximately 1,000 New Zealand children have arthritis.[1]

Rheumatoid arthritis is the most common inflammatory arthritis to affect adult New Zealanders. Its prevalence in the NZ population >19 years (estimated at 3 million in 2006) has been estimated to be 49%, 34% and 18% for the age groups 22–44 years, 45–64 years and >64 years, respectively. The overall prevalence rate has been estimated to be 0.53% of the adult population (over 19).[2]

Direct and indirect costs of arthritis

The total financial cost of arthritis in New Zealand was estimated in 2005 to be $2.35 billion or 1.6% of GDP.[1] Health sector costs of arthritis were estimated to be $563.5 million in 2005; 24% of total financial costs. The burden of disease – the years of healthy life lost because of arthritis – was estimated as over 19,000 Disability-Adjusted Life Years (DALYs) in 2005. When converted into financial terms, this equated to some $2.5 billion in suffering and premature death for those with arthritis in 2005. People with arthritis are 5% less likely to be employed than those without arthritis, based on NZHS data. A total of 25,440 New Zealanders were unable to work because of arthritis, costing an estimated $1 billion in lost productivity that year. In addition, temporary absences from work due to arthritis also imposed costs of some $18 million in 2005. Lost production is the largest cost of arthritis, representing nearly half (46%) of the total financial costs.[1]

Available treatment options

The primary target for the treatment of inflammatory arthritis should be a state of clinical remission. This is defined as the absence of signs and symptoms of significant inflammatory disease activity.

Currently available, relatively inexpensive DMARD regimens are sufficient to control inflammatory disease and maintain long-term function in many patients. However, for the small subset of arthritis sufferers who have disabling pain and progressive damage from uncontrolled inflammatory disease unresponsive to DMARDs, the introduction of the biologic drugs has made remission an achievable goal.

Accumulating clinical data indicate that biologic treatments are extremely cost-effective both in the short- and long-term, and can significantly increase quality of life, provided they are used appropriately – at the right time and in the right way for the relevant populations.[2] In the short-term, direct costs will increase due to the outlay on the drugs, but some costs are off-set even in the short-term by savings in other health care costs such as hospital admissions and surgical interventions. Further cost off-sets to society as a whole are predicted in the long term, as patients remain in the workforce longer. The effect on quality of life is seen immediately after treatment initiation and a higher utility level is maintained while remaining on treatment. The ability of biologic treatments to improve functional capacity and to lower disease activity are the most obvious ways in which they affect quality of life. Published evidence supports the fact that early treatment of RA with biologics results in significant improvement in disease activity and physical function and delays radiographic disease progression.

Until recently, central government funding for tumour necrosis factor (TNF) inhibitors in New Zealand has been limited to adalimumab (Humira®), funded by PHARMAC (New Zealand Pharmaceutical Management Agency) for the treatment of adult patients with inflammatory arthritis, and to etanercept for children with polyarticular JIA. As from 1 November 2010, PHARMAC has widened the access to the biologics so that etanercept can be prescribed for adult patients with RA, ankylosing spondylitis (AS) and psoriasis (PsA), subject to Special Authority criteria that are substantially the same as those that currently apply to adalimumab.[3] Eligible patients will be able to access adalimumab and etanercept in any order. Unfortunately as yet, adalimumab has not been funded for children.

A recent analysis on treatment uptake has shown very low usage of biologic drugs in the indication of RA in New Zealand, noticeably lower than any of the Western European countries (E13) and also substantially lower than in Australia.[2] Only an estimated 3% of the total patient population with RA receives treatment with biologics, compared to around 9–10% in Australia and the UK, and 11% on average in the E13 countries.

Pharmacological properties of etanercept

As a soluble TNF fusion protein, etanercept binds specifically to TNF and blocks its interaction with cell surface TNF-receptors. TNF plays an important role in the inflammatory processes of RA, polyarticular-course JIA, and ankylosing spondylitis and the resulting joint pathology. Elevated levels of TNF are found in involved tissues and fluids of patients with RA, PsA and AS.

Etanercept is administered by subcutaneous injection once or twice weekly. The drug is absorbed slowly after subcutaneous injection, with peak serum concentrations being achieved about 48–60 h after single-dose administration.[4] Studies have consistently indicated that the mean percentage of etanercept available to the target tissues after subcutaneous administration (the absolute bioavailability) is 58–63%.[4] With multiple weekly dosing, etanercept achieves a smooth and uniform steady-state concentration-time profile that is linearly proportional to the weekly dosage administered.[5] The absorption profile of etanercept is similar in patients with RA, AS, or PsA.[6,7] Clinical studies have revealed that pharmacokinetic parameters do not differ between men and women and do not vary with age in adult patients. Etanercept pharmacokinetics are unaffected by concomitant methotrexate in RA patients. No formal pharmacokinetic studies have been conducted to examine the effects of renal or hepatic impairment on etanercept disposition.[8] Population pharmacokinetic analyses predict that the pharmacokinetic differences between the regimens of 0.4 mg/kg twice weekly and 0.8 mg/kg once weekly in JIA patients are of the same magnitude as the differences observed between twice-weekly and weekly regimens in adult RA patients.[8]

Etanercept has generally been well tolerated in clinical trials that have evaluated its efficacy in rheumatic diseases; safety data have been supported by long-term extension studies, by national registries in the EU and the US, and by reports from the US and European agencies.[9]

In controlled trials, withdrawal rates with etanercept were similar to those in the comparator groups; adverse events were generally mild to moderate in intensity.[9] Infections and injection site reactions were the most frequently reported events; upper respiratory tract infections, sinusitis, urinary tract infections, and soft tissues infections were the most commonly reported infections. Serious infections were slightly increased but the occurrence of tuberculosis was less frequent than with anti-TNF monoclonal antibodies (infliximab and adalimumab).[9] Another advantage of etanercept over other TNF inhibitors is that it is not associated with significant development of neutralising antibodies. Moreover, etanercept dosage does not need to be adjusted during coadministration with warfarin, digoxin, or methotrexate.[4]

Efficacy and safety of etanercept in major clinical trials

Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial[10]

Summary: Both clinical remission and radiographic non-progression of disease were achieved by a significantly greater number of patients with early, severe RA treated with a combination of etanercept and methotrexate compared with methotrexate alone during a period of 1 year.

Methods/Results: 524 outpatients with early moderate-to-severe RA were randomised to methotrexate alone (7.5 mg/week titrated to a maximum of 20 mg/week by week 8; n=268) or combined methotrexate (same dose) and etanercept 50 mg/week (n=274). Of the clinically evaluable patients, 136 of 265 (50%) treated with combined therapy achieved DAS28 (disease activity score in 28 joints) remission compared with 73 of 263 (28%) taking methotrexate alone ($p<0.0001$) at week 52. During the same time period, radiographic non-progression (as assessed by joint space narrowing and joint erosion) was achieved by 196 of 246 (80%) patients on combined therapy versus 135 of 230 (59%) on methotrexate-alone ($p<0.0001$). There were no significant differences in the incidences of adverse events between the two treatment groups.

Comment: (Sue Rudge) Remission, both clinical and radiological, has become the aim of clinical trials in the treatment of RA. The results of the COMET trial show that clinical remission is an achievable goal in patients with early severe RA within the first year of therapy with etanercept plus methotrexate. In addition, the results indicated near halting of radiographic progression in 80% of the patients receiving the combination of etanercept and methotrexate compared with 59% in those receiving methotrexate alone.

Functional ability improved, so that by 52 weeks over half the patients on combination therapy had functional disability comparable to that in the healthy population. The incidence of serious events was similar in both groups. Results at the end of the second year showed combination therapy was consistently superior to methotexate therapy alone with no additional safety risk.[11]

These findings reinforce the idea that patients with early disease have distinct benefit from intensive treatment regimens including biologic drugs such as etanercept.

Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis[12]

Summary: Etanercept plus methotrexate showed sustained efficacy through three years and was more effective than monotherapy with either drug in terms of disease remission and inhibition of radiographic progression in the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) study.

Methods/Results: In this double-blind, multicentre study, 682 patients were randomised to receive etanercept 25 mg twice weekly, methotrexate ≤20 mg weekly, or the combination. After three years of treatment, a significantly higher percentage of patients treated with combination therapy had low disease activity (56.3% with DAS28 <3.2) compared with patients in either monotherapy group (DAS28 <3.2 in 33.2% and 28.5% of patients receiving etanercept and methotrexate, respectively; $p<0.01$). The 3-year radiographic results were very similar to those of year 1 and year 2 reported above. Mean changes from baseline at all time points (years 1, 2 and 3) were significantly lower for patients receiving combination therapy or etanercept alone compared with methotrexate alone ($p<0.05$); mean TSS change scores at year 3 were –0.14 for combination therapy versus 1.61 and 5.95 for etanercept and methotrexate, respectively ($p<0.01$). Etanercept and combination treatment were well tolerated with no new safety findings.

Comment: (Sue Rudge) The TEMPO trial differs from COMET in that it looks at 3 different treatment regimens: methotrexate alone, etanercept alone, and methotrexate plus etanercept in combination. It also included patients with much longer disease durations (mean 6.8 years) followed over a 3-year period.

The results showed that combination therapy was much more effective in achieving clinical remission than either monotherapy and that the effect was sustained over a 3-year period.

Importantly, there was a continuous and significant decrease in joint erosion scores, suggesting that improvement in joint damage may be possible in patients treated with the combination therapy.

A network meta-analysis of randomised controlled trials of biologics for rheumatoid arthritis: a Cochrane review[13]

Summary: This updated Cochrane systematic review of the treatment of RA with approved doses of biologic drugs showed that anakinra was less effective than adalimumab and etanercept but that etanercept was safer than adalimumab, anakinra and infliximab in the treatment of RA patients.

Methods/Results: Data were systematically extracted from existing reviews and updated older reviews up to May 2009, using the search term 'rheumatoid arthritis' in the title in the advanced search option. A network meta-analysis was then performed in accordance with the 2008 Cochrane Handbook. Anakinra was shown to be less effective than adalimumab (p=0.046) and etanercept (p=0.015) in achieving ACR50. However, there were significantly fewer withdrawals because of adverse effects among recipients of etanercept compared with adalimumab (p=0.009), anakinra (p=0.003), or infliximab (p=0.002).

Comment: (Sue Rudge) There have been no randomised controlled studies comparing one biologic drug with another in the treatment of RA. This paper provides indirect comparison of the benefit and safety of 6 biologic drugs derived from large double-blind placebo-controlled studies. There were 2 major outcomes; benefit defined as a 50% improvement in the ACR50 and safety defined as the number of withdrawals because of adverse events. Other factors taken into consideration included concomitant use of methotrexate, duration of RA and failure of traditional DMARDs. Etanercept was equally efficacious as other biologic drugs including adalimumab and was associated with fewer withdrawals than anakinra, adalimumab or infliximab.

Etanercept therefore appears equally efficacious and probably safer than other currently used biologics.

The meta-analysis did not address differences in the incidence of anterior uveitis in children taking different biologic drugs. There is some evidence that the new development of uveitis is commoner in those taking etanercept as opposed to those on either infliximab or adalimumab[14] but this remains controversial. Anecdotally, injection site discomfort is also probably greater with etanercept.

Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis[15]

Summary: Etanercept or etanercept plus methotrexate had an acceptable safety and effectiveness profile in JIA.

Methods/Results: Patients aged 2–18 years with rheumatoid factor (RF)-positive or RF-negative polyarthritis, systemic JIA, or extended oligoarthritis received methotrexate alone (≥10 mg/m^2/week, maximum dose 1 mg/kg/week; n=197), etanercept alone (0.8 mg/kg/week, maximum dose 50 mg; n=103) or etanercept plus methotrexate for three years. Physician's global assessment scores and total active joint scores improved from baseline and improvement was maintained for the duration of the study for all treatment groups. Exposure-adjusted rates of adverse events were similar among the three treatment groups (18.3, 18.7 and 21.6 per 100 patient-years in the methotrexate, etanercept and etanercept plus methotrexate groups, respectively).

Comment: (Sue Rudge) The safety and efficacy of etanercept were initially assessed in a double-blind placebo-controlled trial performed by the Pediatric Rheumatology Collaborative Study Group (PRCSG) in the USA and Canada.[16] This involved children with polyarticular disease refractory to treatment with MTX and showed a greater than 30% improvement in ACR core response variables in 80% of the 25 patients who received etanercept compared with 35% of the 26 patients who received etanercept followed by placebo. Eight-year data from this open-label extension study indicated that an ACR Pediatric 70 response was achieved in 100% of the 11 patients still enrolled in the study and receiving etanercept.[17]

The above study shows the results of the largest cohort of JIA patients treated with a biologic agent. It includes all forms of JIA (including polyarticular, extended pauciarticular and systemic disease) and shows that etanercept remains effective over 3 years. The rates of adverse effects were similar across the groups and did not increase with time.

This study is clinically relevant as it reflects the real-life situation in which there are limited therapies for JIA and addresses the concerns about long-term safety in children.

Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression[18]

Summary: Etanercept reduced joint symptoms, improved psoriatic lesions, inhibited radiographic progression, and was well tolerated in patients with PsA.

Methods/Results: 205 patients with PsA were randomised to receive placebo or etanercept 25 mg subcutaneously twice weekly for 24 weeks as blind-labelled therapy, after which all were eligible to receive open-label etanercept in a 48-week extension. Etanercept significantly reduced the signs and symptoms of PsA and psoriasis. At 12 weeks, 59% of etanercept patients met the ACR20 improvement criteria for joint response, compared with 15% of placebo patients (p<0.0001); results were sustained at 24 and 48 weeks. At 24 weeks, 23% of etanercept patients eligible for psoriasis evaluation achieved at least 75% improvement in the Psoriasis Area and Severity Index, compared with 3% of placebo patients (p=0.001). Radiographic disease progression was inhibited in the etanercept group at 12 months; the mean annualised rate of change in the modified total Sharp score was –0.03 unit, compared with +1.00 unit in the placebo group (p=0.0001). Etanercept was well tolerated.

Comment: (Sue Rudge) The central role of TNF in the pathogenesis of psoriatic arthritis is well known. Earlier studies have shown that etanercept improved the articular and cutaneous manifestations of PsA[19] but this is the first study to evaluate the effect on radiographic progression. This was assessed over 6- and 12-month periods using the modified Sharp score. Patients receiving placebo had progressive joint destruction at 6 and 12 months, whereas most patients in the etanercept group had inhibition of radiographic progression comparable to results shown with etanercept in RA.

Erosive change in PsA can be very destructive and the effect of etanercept on radiographic disease progression has important implications for long-term disease outcome.

Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized controlled trial[20]

Summary: Etanercept proved to be highly effective as well as well tolerated in adult patients with moderate to severe active AS.

Methods/Results: This cohort of patients received either etanercept 25 mg (n=138) or placebo (n=139) subcutaneously twice weekly for 24 weeks. At 12 weeks, the Assessments in Ankylosing Spondylitis 20% response (ASAS20) was achieved by 59% of etanercept recipients and by 28% of placebo recipients (p<0.0001); corresponding values at 24 weeks were 57% and 22% of patients, respectively (p<0.0001). All individual ASAS components, acute-phase reactant levels, and spinal mobility measures were also significantly improved. The safety profile of etanercept was similar to that reported in studies of patients with RA or PsA. The only adverse events that occurred significantly more often in the etanercept group were injection site reactions, accidental injuries, and upper respiratory tract infections.

Comment: (Sue Rudge) Of all the inflammatory arthropathies, AS has always been the most challenging to treat with fewer therapeutic options. NSAIDs produce only moderate symptomatic benefit and DMARDs have only limited efficacy on peripheral symptoms and no effect on progressive loss of spinal mobility.

This 24-week, placebo-controlled study showed dramatic improvement in the ASAS20 and in all individual ASAS components, including spinal mobility measures. This suggests that etanercept may modify the disease as well as control the symptoms of AS.

Later MRI studies have shown decreased spinal inflammation in etanercept-treated patients[21] and a large multicentre study has confirmed the safety and efficacy of etanercept in AS for up to 192 weeks.[22]

Concluding remarks - Dr Sue Rudge

Etanercept was the earliest TNF-blocker introduced worldwide for the treatment of inflammatory arthritis. It was licensed for use in the USA for moderate to severe RA in 1998, polyarticular JIA in 1999, PsA in 2002 and AS in 2003. In NZ it has been funded for JIA since 2004 and in November 2010 PHARMAC widened the access criteria to include adults with RA, AS and PsA. Overall there has been an estimated 2.25 million patient-years of collective clinical experience using etanercept in patients with inflammatory arthritis.

As the above studies demonstrate, it has been found to be efficacious in all forms of inflammatory arthritis, leading to a sustained clinical response together with radiographic evidence of non-progression. It also has a remarkably good safety record maintained over 18 years.

The recent introduction of a once-weekly auto-ject pen and PHARMAC's widened access criteria provide NZ physicians and patients with a welcome choice in both first- and second-line biologic therapy.

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