Review

Etanercept in spondyloarthropathies.
Part II: safety and pharmacoeconomic issues

S. D’Angelo¹,², C. Palazzi¹, F. Cantini³, E. Lubrano⁴, A. Marchesoni⁵, A. Mathieu⁶, C. Salvarani⁷, R. Scarpa⁸, A. Spadaro⁹, I. Olivieri¹

¹Rheumatology Department of Lucania, San Carlo Hospital of Potenza, Potenza; ²Department of Health Sciences, University of Molise, Campobasso; ³Rheumatology Unit, 2nd Division of Medicine, Prato Hospital, Prato; ⁴Academic Rheumatology Unit, Department of Health Science, University of Molise, Campobasso, Italy; ⁵UOC Day Hospital di Reumatologia, Istituto Ortopedico G. Pini, Milano; ⁶Chair of Rheumatology, Department of Medical Sciences, University of Cagliari, Cagliari; ⁷Rheumatology Unit, Arcispedale S. Maria Nuova, Reggio Emilia; ⁸Academic Rheumatology Unit, University of Naples Federico II, Napoli; ⁹Department of Internal Medicine and Medical Specialties, Division of Rheumatology, “Sapienza” University of Rome Roma, Italy.

Salvatore D’Angelo, MD
Carlo Palazzi, MD
Fabrizio Cantini, MD
Ennio Lubrano, MD
Antonio Marchesoni, MD
Alessandro Mathieu, MD
Carlo Salvarani, MD
Raffaele Scarpa, MD
Antonio Spadaro, MD
Ignazio Olivieri, MD

Please address correspondence to:
Dr Ignazio Olivieri,
Rheumatology Department of Lucania,
San Carlo Hospital,
Contrada Macchia Romana,
85100 Potenza, Italy.
E-mail: l.olivieri@ospedalesancarlo.it

Received on April 16, 2011; accepted in revised form on July 11, 2011.
© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2011.

Key words: etanercept, ankylosing spondylitis, psoriatic arthritis, safety, pharmacoeconomy

ABSTRACT
Etanercept (ETN) and other anti-TNF-α agents have revolutionised the management of spondyloarthropathies (SpA). With the increasingly widespread and prolonged use of these drugs an assessment of their long-term safety is extremely important. An additional concern regarding biological agents is their higher costs compared with conventional drugs. We examined safety data regarding ETN from clinical reports, clinical trials, review articles, databases and registries. In addition, evidence was reviewed about the cost effectiveness of ETN in the treatment of patients with SpA.

Our review suggests that ETN is well tolerated as long-term, continuous treatment of SpA with a favourable risk-benefit ratio maintained from 4 to 5 years. Diversity in structure and mode of action could explain some differences in the safety profile of ETN with respect to the other anti-TNF agents. In particular, ETN is less immunogenic and is less likely to induce tuberculosis re-activation than the other TNF-α antagonists.

Although ETN is considerably more expensive than conventional therapy, it reduces direct and indirect costs associated to SpA by improving disease activity and quality of life. Recent pharmacoeconomic studies have demonstrated its cost-effectiveness in the treatment of SpA.

Introduction
The anti-tumour necrosis factor (TNF) α blocking agents have revolutionised the management of spondyloarthropathies (SpA). Compared to traditional DMARDs, they are superior in reducing signs and symptoms of inflammation and in improving quality of life and functional status. In addition, these drugs inhibit the progression of structural damage in peripheral joints (1).

With the increasingly widespread and prolonged use of anti-TNF-α agents, an assessment of their long-term safety is extremely important. An additional concern regarding the biological agents is their higher costs compared with conventional drugs.

Several studies have reported on the efficacy, the safety, and the costs of etanercept (ETN). This paper reviews the safety profile and the pharmacoeconomic evaluation of ETN in the treatment of patients with SpA. Efficacy issues are addressed in part I of this review (1).

Safety
ETN, a fully-human soluble TNF receptor, is a fusion protein composed of two extracellular domains of the human p75-TNF-receptor (sTNFRI), linked to the Fc portion of human IgG1. The two sTNFRII arms of ETN bind two of the three receptor-binding sites on the TNF trimer in a 1:1 ratio (2), leaving the third receptor binding site open (3). This feature and the fast association/dissociation rates of the sTNFRII with TNF-α suggest that ETN may only transiently neutralise the activity of an individual TNF-α molecule (4). Nevertheless, at low concentrations of soluble TNF-α, ETN would more effectively neutralise TNF-α than would infliximab (IFX) or adalimumab (ADA). An interesting point is the relationship between TNF-α blockers and interferon-γ (IFN-γ) production. In fact, IFN-γ expression was inhibited by IFX, but not by ETN (5, 6), suggesting that granuloma-dependent infection risk may therefore reflect this ability to inhibit both TNF-α and indirectly IFN-γ (7).
ETN differs from other TNF-α blockers regarding the capacity to inhibit members of the lymphotoxin (LT) family, namely soluble LTα3 involved in immune functioning and inflammation (7-9). Moreover, current evidence suggests that TNF-α antagonists have a dual function and can act as antagonists by blocking transmembrane TNF-α or as agonists by initiating reverse signal, leading to apoptosis, cell activation or cytokine suppression (8). ETN does not induce apoptosis in some tissues (e.g. gastrointestinal mucosa), while in synovium, both anti-TNF-α soluble receptor and monoclonal antibodies seem to cause apoptosis (7). In contrast with ADA or IFX, ETN does not activate complement-dependent cytolysis and antibody-dependent cell-mediated cytotoxicity. In fact, ETN contains the Fc portion of IgG1, but does not fix the complement, perhaps because steric hindrance prevents C1q binding (7). The hypothesis of different steric accessibility of the Fc region of ETN could explain also the markedly shorter plasma half-life (4 days) of ETN versus monoclonal antibodies or other Fc fusion proteins (8).

Finally, ETN differs from other TNF-α blockers in its lower immunogenicity as confirmed by a recent study assessing antibodies against ETN in patients with ankylosing spondylitis (AS) (10). This difference could be due to a less immunogenic structure since only the fusion part of the molecule can contain immunogenic epitopes. In contrast, the monoclonal antibodies IFX and ADA have more epitopes within the variable region of the antibody to which an immune response can be directed. The above reported findings could explain some differences in safety profile of ETN with respect to IFX and ADA.

Table 1. Main adverse events that occurred during etanercept AS and PsA RCTs and AS OLE.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>AS-RCT (11) (24 weeks)</th>
<th>AS-RCT (14) (12 weeks)</th>
<th>AS-OLE (12) (192 weeks)</th>
<th>AS-OLE (13) (108 weeks)</th>
<th>PsA-RCT (15) (24 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>ETN 138 (pts)</td>
<td>PL 139 (pts)</td>
<td>ETN 151-5 (pts)</td>
<td>PL 51 (pts)</td>
<td>ETN 257 (pts)</td>
</tr>
<tr>
<td></td>
<td>30%*</td>
<td>9%</td>
<td>23%-21%</td>
<td>12%</td>
<td>22%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>20%*</td>
<td>12%</td>
<td>8%-8%</td>
<td>14%</td>
<td>45%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>6%</td>
<td>6%</td>
<td>&lt;3%</td>
<td>&lt;3%</td>
<td>NA</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8%</td>
<td>9%</td>
<td>3%-4%</td>
<td>0%</td>
<td>17.5%</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>4%</td>
<td>7%</td>
<td>&lt;3%</td>
<td>&lt;3%</td>
<td>15%</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>12%</td>
<td>3%-4%</td>
<td>0%</td>
<td>20%</td>
</tr>
<tr>
<td>Rash</td>
<td>8%</td>
<td>6%</td>
<td>&lt;3%</td>
<td>&lt;3%</td>
<td>NA</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>&lt;3%</td>
<td>&lt;3%</td>
<td>NA</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>&lt;3%</td>
<td>&lt;3%</td>
<td>16%</td>
</tr>
</tbody>
</table>

AS: ankylosing spondylitis; PsA: psoriatic arthritis; RCT: randomized clinical trials; OLE: open label extension; ETN: etanercept; PL: placebo.

*significantly different from placebo.

In conclusion, in the previously cited RCTs and OLEs, ETN showed a good safety profile in SpA and, for PsA, this has been confirmed by a meta-analysis (17).

Post-marketing surveillance and registers are a useful source of safety data of unselected patient populations. A Spanish TNF-α antagonist register included 1,524 patients with SpA, of whom 657 with AS and 570 with PsA (18). Most of the patients were on IFX but there was an exposure to ETN of 134 and 325 patient-years for AS and PsA, respectively. At three years, the drug survival rate of all of the three anti-TNF-α agents was 0.76 for AS and 0.73 for PsA, with AE incidence of 45.4% of the therapy discontinuations.

Interestingly enough, the AE-incidence rate per 100 patient-years of exposure in all of the 507 SpA patients treated with ETN was lower than 1, with the exception of the infection rate, which, however, was only 1.01. A Norwegian register of DMARD prescription (including biologic therapies) collected 172 patients with PsA and 249 with AS receiving TNF-α antagonists, of whom 96 and 122, respectively, were given ETN as first biologic (19). The 1-year withdrawal rates of this drug were 24% for PsA and 24.6% for AS. AEs were responsible for 69.2% and 43.6% of discontinuations of the anti-TNF-α agents (as a whole) in PsA and AS, respectively. About 45% of 261 PsA patients from the South Swedish
Arthritis Treatment Group Register receiving TNF-α inhibitors were treated with ETN showing a rate of SAEs per 100 treatment-years of about 5.5 (20). In addition, this study suggested that in patients receiving anti-TNF-α agents in combination with MTX the survival rate on therapy was higher than in patients on TNF-α blockers alone, due to a lower rate of AEs. However, this result was not confirmed by a study on PsA patients treated with ETN showing the same retention rate regardless of concomitant use of MTX (21). Recent data from the British Society of Rheumatology Biologics Register confirmed that PsA patients treated with anti-TNF-α agents, mainly ETN (56% of the total), have a safety profile similar to that seen in a control cohort of patients receiving DMARD therapy (22, 23).

In conclusion, the data from the few existing registers seem to indicate that in standard clinical settings of patients with PsA and AS, anti-TNF-α agents in general, and ETN in particular, are more often responsible for drug discontinuations than in RCTs but, nevertheless, these molecules have a good safety profile. If the low frequency of AEs, especially AEs, in SpA patients taking ETN is encouraging, major concerns come from some AEs which have been rarely described during therapies with this drug and the other TNF-α antagonists. Reactivation of tuberculosis (TB), re-activation of hepatitis B virus (HBV) infection, congestive heart failure (CHF), demyelinating neurological disorders, aplastic anaemia, pancytopenia, vasculitis, immunogenicity, and exacerbation or induction of psoriasis are well-known class-effects of all of the TNF-α inhibitors, and have been seen both in rheumatoid arthritis (RA) and SpA patients (24-26). TB cases have decreased dramatically after the institution of TB screening but they have not disappeared. As false-negative results of the screening and first infection can occur, careful vigilance for TB is still required. It has recently been confirmed that ETN is less likely to induce TB re-activation than the other TNF-α antagonists (27-29). In addition, ETN did not induce any TB reactivation in a cohort of 84 patients, including AS and PsA patients, at high risk for TB infections (PPD-positive patients) (30).

HBV re-activation, CHF, and demyelinating diseases are potential adverse events of anti-TNF-α therapy that can occur regardless of the underlying condition. Vasculitis and immunogenicity are much more likely to occur in RA patients than in SpA patients (25, 31). It has been suggested that ETN might be less immunogenic than the other TNF-α antagonists, especially in AS (10, 31). Exacerbation or induction of psoriasis, usually of the pustular type, is a paradoxical effect of TNF-α inhibition that can occur in any disease (26). Interestingly enough, it seems that while the anti-TNF-α monoclonal antibodies can induce new onset psoriasis, ETN is more likely to cause flares of pre-existing disease (32). The relationship between malignancy and anti-TNF-α drugs is still an unresolved issue. In RA some studies did not find an increased incidence of lymphoma or solid cancers in patients taking TNF-α inhibitors, while others did (27). In a recent systematic review, PsA and psoriatic patients treated with anti-TNF agents showed increased rates of non-melanoma skin cancer (33). This risk was increased by treatment with methotrexate, cyclosporine and phototherapy.

A number of confounding factors, the low rate of malignancies, and the long time period needed for a cancer to develop have not allowed to give a definite answer to this important question. Although the data on malignancy in SpA patients treated with anti-TNF agents are scant, the strong immunosuppressive effect of these drugs implies the potential risk of cancer induction. Acute uveitis, Crohn’s disease, and sarcoidosis are other AEs that have been rarely associated with ETN therapy in SpA patients. Several anecdotal reports and a study using observations from two drug event databases have suggested that ETN may be responsible for flares or new occurrences of acute anterior uveitis (AU) (34). In contrast, other data have shown that ETN may prevent acute uveitis in AS, although less effectively than IFX (35). Considering all the available data, it seems likely that ETN is not as effective as the anti-TNF-α monoclonal antibodies in treating and preventing acute uveitis. In contrast to the other two TNF-α inhibitors, ETN is not effective in controlling active Crohn’s disease (36). Furthermore, several case reports have been published suggesting the possibility that this drug unmasks silent inflammatory bowel disease in patients with SpA (36, 37). Finally, a few case reports have been published on the development of sarcoidosis during ETN therapy in both RA and SpA patients (38).

An interesting issue about the safety profile of anti-TNF-α therapy is older age. It is not uncommon to prescribe this therapy in elderly patients and there is concern that these patients may be more prone to develop AEs. A retrospective analysis of trials on ETN in RA, AS, and PsA has shown that in patients ≥65 years the rate of AEs and SAEs was not higher than in the younger patients (39). It should be remembered, however, that patients with co-morbidity are usually excluded from RCTs.

Neither animal studies nor prospective, controlled human studies have shown an increased rate of adverse outcomes after exposure to ETN during pregnancy (40). Therefore, experts suggest that the drug can be continued until an expected menstruation is missed or after a positive pregnancy test. In addition, ETN may be continued during pregnancy when strongly indicated (41, 42).

Pharmaeconomic aspects

ETN and the other TNF-α agents can offer better clinical response in AS and PsA compared with traditional DMARDs and NSAIDs but they are associated with greater costs and therefore not readily available to all patients (43, 44). The annual cost of ETN using either the twice-weekly dose of the 25-mg vial or the one-weekly dose of the 50 mg vial is $9,295 (NICE technology appraisal guidance 199). Illness costs in AS and PsA were found high even without anti-TNF-α inhibitors and not much different than those in RA and systemic lupus erythematosus (45-47). A recent paper addressed the cost-effectiveness of anti-TNF agents
in a real-world setting for the treatment of patients with RA, PsA and AS (48). The estimate of cost-effectiveness was based on the number needed to treat (NNT) to achieve a minimal clinically important difference (MCID) in HAQ scores. The NNT were similar for the 3 diseases studied (1.94 for RA, 1.88 for PsA, and 2.30 for AS).

Treatment of AS or PsA patients with anti-TNF-α blockers are supported, on the one hand, by expert-and evidenced-based guidelines that have been made available for their use, on the other hand, by pharmacoeconomic studies performed with the purpose of demonstrating their cost-effectiveness (49-59). Ara et al. examined cost and benefits associated with long-term ETN treatment in patients with severe AS in the UK by using a mathematical model (50). Over a 25-year horizon, therapy with ETN plus NSAIDs gave 1.58 more quality-adjusted life years (QALYs) at an additional cost of £35,978, when compared with NSAID treatment alone, thus resulting in an incremental cost-effectiveness ratio (ICER) for ETN of £22,700 per QALY gained, which is under the willingness-to-pay threshold of £30,000 per QALY gained identified by the National Institute of Clinical Excellence (NICE) (52). A recent German study, aiming to assess the cost-effectiveness of ETN compared with usual care in AS patients, found an ICER of €54,815 per QALY calculated over a 25-year horizon and from a social health insurance perspective (57). These data were higher than in the UK but comparable with those calculated in patients with RA in Germany. As far as PsA is concerned, Bansback and co-workers estimated the potential long-standing benefits on health status of ETN and evaluated its long term effectiveness in comparison with conventional DMARDs (53). Data coming from randomised control trials and from a local cohort of patients were utilised to analyse health state utilities and long-lasting disease progression. Over the 10 years period, ETN gave a cost per QALY gained of about €30,000 in comparison with leflunomide or combined therapy with MTX and cyclosporine. Bravo Vergel et al. evaluated the cost-effectiveness of ETN, IFX and so called “palliative care” (i.e. no active therapy equivalent to placebo) from a UK National Health Service (NHS) perspective (55). The authors used Bayesian statistical methods to synthesise evidence from three Phase III trials, identified through a systematic review, which allowed the estimation of the relative efficacy of ETN and IFX despite the absence of head-to-head comparison trials. At a 10-year time horizon, the ICER for ETN compared with palliative care was £26,361 per QALY gained for the best-case (equal to gain) rebound scenario and £30,628 for the worst-case (equal to natural history progression). The Psoriatic Arthritis Cost Evaluation (PACE) study used a different approach. Unlike the previous cost-effectiveness studies on TNF-α blocking agents, which used data from published international trials, this study was performed in a clinical practice setting (56). The aim was to evaluate costs, benefits and cost-effectiveness of the class of TNF-α antagonists over 1 year of follow-up. A total of 107 patients with different forms of PsA showing inadequate response to conventional treatment were given anti-TNF-α agents, mainly ETN (87%). At the end of 12 months of follow-up, there was a significant increase of direct costs due to an increase of drug cost caused by anti-TNF-α agents, that was only partially counterbalanced by the decrease in indirect costs. However, a gain of 0.12 QALY resulted in a cost per QALY gained of €40,876 for the NHS and of €37,591 for the society. The acceptability curve showed that there would be a 97% likelihood that anti-TNF-α therapy would be considered cost-effective at the willingness-to-pay threshold of €60,000 per QALY gained proposed for Italy. One strength of the Italian study is the demonstration that anti-TNF-α therapy is cost-effective in the short term in clinical practice. A recent Korean retrospective study on AS patients showed that extending dosing interval of ETN (25 mg up to 12.1±7.0 days) resulted to be still effective (59). These data open new possible scenarios concerning the pharmacoeconomic aspects of ETN therapy.

In conclusion, although ETN is an expensive drug, recent pharmacoeconomic studies have demonstrated that it is a cost-effective treatment for SpA.

**Conclusions**

The introduction of ETN and other anti-TNF-α agents has revolutionised the therapeutic management of SpA. These drugs improve symptoms and signs, enhance quality of life and functional capacity, and slow the progression of the structural damage in peripheral joints. Data from OLE and registries suggest that ETN is well tolerated as a long-term, continuous therapy for the treatment of SpA with a favourable risk-benefit ratio and no cumulative toxicity for up to 5 years.

ETN is considerably more expensive than conventional therapy but, by inducing improvements in disease activity and quality of life, it reduces direct and indirect costs due to SpA. In the past few years, several studies have showed the cost-effectiveness of ETN suggesting public health systems to reimburse anti-TNF-α therapy in order to reduce the costs of illness of SpA.

**References**


7. FORST DE, WALLIS R, BRODER M, BEENHOUWER DO: Tumor necrosis factor
antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection.


18. FIORENTINO DF: The yin and yang of TNF-α drugs in rheumatic diseases, 2008.


33. BOSKER P: The yin and yang of TNF-α drugs in rheumatic diseases, 2008.


43. BOSKER P: The yin and yang of TNF-α drugs in rheumatic diseases, 2008.


