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REVIEW

# Etanercept in the Treatment of Psoriasis: The Emerging Evidence of its Therapeutic Value

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**Abstract:** Etanercept is a fusion protein of soluble TNF receptor type II with human IgG Fc fragment, whose use was approved for psoriasis by the FDA and by the EMEA. It neutralizes the proinflammatory effects of TNF-α, a cytokine with a pivotal role in the pathogenesis of psoriasis, preventing binding to its receptors. The aim of our study was to review the emerging evidence of the therapeutic value of etanercept in the treatment of psoriasis. We found that since its approval, several randomised clinical trials have shown its efficacy in the short and long-term, both in a continuous and interrupted course of therapy. Data deriving from these studies have also suggested an acceptable safety profile, as found also in studies conducted on its use in other autoimmune diseases. Etanercept also seems to be efficacious and safe when administered in a combined treatment with other traditional medications and after switching from another biological drug. Moreover, despite its high costs it does seem to be a cost-effective treatment.

**Keywords:** psoriasis, etanercept, efficacy, safety, anti-TNF-α agent, combined treatment

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## Introduction

Psoriasis is a chronic, inflammatory skin disorder that affects 2%–3% of the world population and is associated with an inflammatory arthritis in 5%–30% of patients in different samples.[1]

For several years, etiopathogenesis of psoriasis had been primarily related to an alteration of keratinocyte differentiation and/or proliferation. However, almost 20 years ago it became evident that T cells play a pivotal role in the pathogenesis of psoriasis.[2] More recently it has been demonstrated that a dysregulation of innate immunity is an early event in the pathogenesis of the disease and leads to the production of several cytokines, which facilitate T cell recruitment into the skin.[3] The infiltrating lymphocytes are subsequently responsible for a cascade of events that finally lead to keratinocyte proliferation.[4]

Based upon the immunopathogenetic background of psoriasis the various therapeutic options consist predominantly of immunosuppressive drugs. Various therapeutic approaches are adopted according to different guidelines based on the severity and extension of psoriasis, the presence of arthritis, and the QoL impairment.[5,6] Topical treatments (ie, corticosteroids, vitamin D analogs, tazarotene); phototherapy with ultraviolet B (UVB) rays or with psoralen and ultraviolet A radiation (PUVA); systemic treatments (eg, acitretin, methotrexate—MTX, cyclosporine—CsA, fumaric acid esters); and "biologics" (including tumor necrosis factor [TNF]-α blockers) are all effective in different ways and to different extents. These last few therapeutic options have been introduced following recent advances in the understanding of the pathogenesis of psoriasis. In particular, TNF-α blockers are molecules that interfere with specific steps in the cytokine cascade (where TNFα is the main actor) and which contribute to the development of skin lesions. Among these drugs, etanercept is a fusion protein of soluble TNF receptor Type II (TNF-RII or p75) with human IgG Fc fragment, whose use was approved for psoriasis by the FDA in 2004 and then in 2005 by the EMEA (European Medicines Agency). It neutralizes the proinflammatory effects of TNF-α, a cytokine with a pivotal role in the pathogenesis of psoriasis, preventing binding to its receptors. The approved dosage is 50 mg subcutaneously either once or twice weekly—according to the opinion of the physician—for 12 weeks, and 50 mg weekly thereafter. According to the EMEA, etanercept, like the other biologics, can be prescribed to treat moderate-to-severe psoriasis when traditional systemic therapies are either ineffective, contraindicated or associated with side effects. Moderate-to-severe psoriasis is diagnosed as a Psoriasis Area and Severity Index (PASI)[7] score or a percentage of Body Surface Area (BSA) $>10$.[8]

The aim of our study was to review the emerging evidence of the therapeutic value of etanercept in the treatment of psoriasis.

## Search Strategy

The PubMed databases were searched in October 2010 using the terms 'psoriasis' and 'etanercept'. Searches were limited to studies published in English. References were checked for additional sources. From the list obtained, we evaluated only articles which made reference to these 6 main areas: "randomised clinical trials", "long-term vs. interrupted therapy", "switch from another biological treatment", "combined treatment", "safety data" and "pharmaeconomical considerations".

We found 834 articles, of which 77 have been considered for our review. In particular, we evaluated 15 manuscripts for the first section, 8 for the second, 5 for the third, 17 for the fourth, 21 for the fifth and 11 for the final one. A few articles have been cited in more than one section.

## Randomized Clinical Trials

The first evidence of the efficacy of etanercept in the treatment of psoriasis derived from a randomised double-blind placebo controlled 12 week study.[9] Mease et al administered 25 mg twice-weekly (BIW) subcutaneous injections to 30 patients with psoriatic arthritis and psoriasis. Out of nineteen of those patients who could be assessed for psoriasis by means of PASI score, five (26%) achieved an improvement of 75% (PASI75), compared with none of the placebo-treated patients. Moreover, the median PASI improvement was 46% in etanercept-treated patients versus 9% in the control group. The drug was generally well tolerated. Following this study, extensive evidence of the efficacy of etanercept for cutaneous disease in patients treated for a concomitant psoriatic arthritis[10] was reported and in 2003 the results of a clinical trial involving patients affected by psoriasis with or without a concomitant arthritis were published.[11] This was

a randomized, double-blind, placebo-controlled, multicenter study, evaluating etanercept 25 mg, subcutaneously BIW for 24 weeks in 57 psoriatic patients. The authors found that after 12 and 24 weeks of treatment, 30% and 56% of patients respectively had achieved PASI75. The first trial evaluating the best dosage regimen of etanercept in the treatment of psoriasis was undertaken by Leonardi et al.[12] This was a 24-week, double-blind study, involving 652 patients who received a placebo or etanercept subcutaneously at a low dose (25 mg) once weekly (QW)), a medium dose (25 mg BIW), or a high dose (50 mg BIW). After 12 weeks, the authors reported that a PASI75 improvement was obtained respectively in 4, 14, 34 and 49 percent of the patients. They also showed that the clinical response continued to improve with longer treatment at the medium etanercept dosage (25 mg BIW). At week 24, PASI75 was obtained in 25 percent of the patients in the low-dose group, 44 percent of those in the medium-dose group, and 59 percent in the high-dose group. The efficacy of etanercept was also confirmed by the quality-of-life measures.[13] No serious side effect was recorded. In 2005, Papp et al confirmed that a 12 week induction therapy at higher dosage allowed the attainment of a more meaningful clinical improvement with no apparent decrease in efficacy after dose reduction.[14] In fact, in their placebo controlled study, 583 patients were randomly assigned to receive etanercept BIW at a dose of 50 mg or 25 mg by subcutaneous injection in a double-blind fashion. During the second 12 weeks, all patients received etanercept 25 mg BIW. They found at week 12 that PASI75 was achieved by 49% of patients in the etanercept 50 mg BIW group, 34% in the 25 mg BIW group; at week 24 (after an additional 12 weeks of an open-label 25 mg etanercept BIW treatment for both groups), PASI75 was achieved by 54% and 45% of patients respectively. This trend was also confirmed by data assessing the patient-reported outcomes.[15]

Other authors have evaluated the efficacy and safety of different dosage regimens. In 2006, Tyring et al reported the findings of a double-blind placebo-controlled study involving 618 patients with moderate to severe psoriasis who received 50 mg BIW etanercept for a long-term, 96 week treatment. PASI75 was achieved in 47% of patients at week 12 and was associated with the relief of fatigue and symptoms of depression as assessed by the evaluation of the relative clinical scales.[16] The long-term efficacy of a continued treatment with etanercept 50 mg BIW was then sustained by 51.1% of patients who maintained PASI75 improvement up to week 96.[17] Other evidence regarding the long-term efficacy of etanercept in psoriasis comes from the study by Kreuger et al.[18] They evaluated the effectiveness of continuing treatment with etanercept beyond 24 weeks in patients who initially had not achieved at least a 50% improvement of baseline PASI in a previous study by Gottlieb et al.[11] In this open-label study they showed that more than half of patients who initially had an inadequate response to treatment achieved satisfactory responses by continuing etanercept therapy. Data were recorded until week 60. Following these previous studies on the use of etanercept at a dosage of 25 mg QW or BIW or 50 mg BIW, in 2008 Van der Kerkhof et al showed also the

**Table 1.** Data about efficacy deriving from multiple randomised clinical trials.

| Dosage regimen | | No of patients enrolled | Percentage of patients achieving PASI75 | | | Reference |
|---|---|---|---|---|---|---|
| First 12 wks | After wk 12 | | At wk 12 | At wk 24 | After wk 24 | |
| 25 mg BIW | – | 30 | 26 | – | – | 9 |
| 25 mg QW | 25 mg BIW | 652 | 14 | 25 | – | 12 |
| 25 mg BIW | | | 34 | 44 | – | |
| 50 mg BIW | | | 49 | 59 | – | |
| 25 mg BIW | 25 mg BIW | 57 | 30 | 56 | – | 11 |
| 50 mg BIW | 25 mg BIW | 583 | 49 | 54 | – | 14 |
| 25 mg BIW | | | 34 | 45 | – | |
| 50 mg BIW | 50 mg BIW | 618 | 47 | 60 | 51 (wk 96) | 17 |
| 50 mg QW | 50 mg QW | 142 | 37 | 71 | – | 19 |
| 0.8 mg pro Kg QW | 0.8 mg pro Kg QW | 211 (4–17 aged) | 57 | 68 (wk 36) | 61 (wk 96) | 22 |

**Table 2.** Summary chart from each section in the paper.

| | |
|---|---|
| Randomised clinical trials | Several studies have shown the efficacy of etanercept in the short and long-term. |
| Long-term vs. interrupted therapy | Several studies have shown the efficacy both in a continuous and interrupted course of therapy. |
| Switch from an other biological treatment | Etanercept seems to be efficacious and safe when administered after switching from another biological drug. |
| Combined treatment | Etanercept seems to be efficacious and safe when administered in a combined treatment with other traditional medications, particularly methotrexate and acitretin. |
| Safety concern | Data deriving from several studies and national database have also suggested an acceptable safety profile, as found also in studies conducted on its use in other autoimmune diseases. |
| Pharmaeconomy | Despite its high costs it seems to be cost-effective. |

efficacy of a therapeutic regimen with etanercept[19] in a double-blind, placebo controlled, randomised study where they enrolled 142 patients who received etanercept 50 mg QW. PASI75 was achieved by 37.5% and 71.1% patients respectively at week 12 and 24. Data of efficacy in this study were also mirrored by the improvement in quality of life.[20] A further study showed that 50 mg QW was an appropriate regimen for treatment of joint and tendon symptoms in AP patients, while treatment with etanercept 50 mg BIW may allow for more rapid clearance of skin lesions.[21] In fact, in this last randomised double blind multicentre 24 week study involving 752 outpatients with both psoriasis and psoriatic arthritis, the authors reported that a significantly higher percentage of patients achieved PASI75 improvement (55% vs. 36% at week 12 and 70% vs. 62% at week 24) in the group treated with etanercept 50 mg BIW for the first 12 weeks therapy than in the group treated with 50 mg QW for all 24 weeks.

All of the studies reported above involved patients older than 18. In 2008, the first randomised double blind clinical trial involving paediatric patients was published.[22] Paller et al enrolled 211 patients with psoriasis (4 to 17 years of age) and assigned them to receive 12 QW subcutaneous injections of placebo or 0.8 mg of etanercept per kilogram of body weight (to a maximum of 50 mg), followed by 24 weeks of QW open-label etanercept. They found that at week 12, 57% of patients receiving etanercept achieved PASI75, compared with 11% of those receiving the placebo. Moreover, at week 36, the rate of PASI75 was 68% for patients initially assigned to etanercept. Forty-two percent of the 69 patients who at week 36 withdrew treatment lost the clinical response. In this study, four serious adverse events (including three infections) occurred in three patients after the first 12 weeks of treatment, all of which resolved without significant consequences. Paller et al also published the data on long-term safety and efficacy of this regimen. They reported that, at week 96, 61% of patients maintained PASI75 improvement without any additional serious side effects being registered.[23]

Finally, 7 randomized clinical trials have been reported in the literature, involving almost 2293 patients, enrolled for periods ranging from 12 up until 96 weeks. Each study shows a statistically significant major efficacy of etanercept when compared to a placebo in the treatment of psoriasis. They also showed that the dosage of 50 BIW seems to be the most efficacious and that a continuous treatment allows the clinical improvement obtained in the first weeks to be maintained.

## Long-term vs. Interrupted Therapy

Although the efficacy and safety of a long-term course of therapy of up to 4 years with etanercept has been widely documented,[24] at times dermatologists may, for various reasons, opt to use etanercept intermittently. This could occur in situations such as preparation for surgery, for economic reasons or simply to prevent the patient from being exposed to further potential toxic risks. Various authors have shown the efficacy even of this intermittent therapeutic regimen. In 2006, Gordon et al reported the results of their study evaluating the safety and efficacy of etanercept re-treatment in psoriasis.[25] They enrolled patients of a previous reported 24-week randomized,

placebo-controlled, double-blind study.[11] Patients who responded at week 24 (achieving at least PASI50) discontinued etanercept until disease relapse (loss of the previous improvement); they were then retreated with etanercept at the same dosage as previously. The authors found that the psoriasis relapsed on average 3 months after etanercept discontinuation. However, the re-administration of the treatment induced an improvement similar to that obtained with the first cycle of therapy. Subsequently, Moore et al performed a randomized, open-label study, based on the Etanercept Assessment of Safety and Effectiveness (EASE) on more than 2500 psoriasis patients from 325 community dermatology sites in the United States.[26] All patients received uninterrupted etanercept 50 mg BIW during the first 12 weeks, followed by either continuous or interrupted etanercept 50 mg QW in the next 12 weeks. In the latter group, therapy was discontinued at week 12 and then resumed at week 16 or 20, upon relapse of the disease and continued through week 24 at the dosage of etanercept 50 QW. The proportion of responders at week 24 was greater in the continuous group than in the interrupted group and safety was comparable. The authors concluded that although continuous etanercept therapy provided optimal benefits, patients who respond well to etanercept and need to discontinue the treatment may reinitiate it with a high probability of recovering similar response and without increased safety risks. A study subsequently evaluated in these same patient groups the patient-reported outcomes and health-care resource utilization data.[27] No meaningful differences between continuous and interrupted treatment were detected but both produced sustained and clinically significant improvement.

Ortonne et al realized a study in 711 patients with moderate-to-severe plaque psoriasis, randomising them to receive either continuous etanercept 25 mg BIW or paused etanercept for 54 weeks.[28] The paused group received etanercept 50 mg BIW for no more than 12 weeks until they reached a Physician Global Assessment (PGA) of 2 or less; treatment was then stopped; upon relapse (PGA $\geq$ 3), etanercept was resumed at 25 mg BIW until a PGA of 2 or less was regained. At week 54, the clinical improvement was significantly higher in the continuous etanercept therapy group than in the intermittent etanercept therapy group, as shown by the mean PGA and PASI score. A similar trend was also deduced from patient reported outcomes.[29] In this study, 7.5% of patients had serious adverse events, four patients in particular (two per group) had serious infections. In 2009, Ortonne et al then realized a post-hoc analysis of patients treated with the interrupted therapy to evaluate the long-term efficacy of re-treatment.[30] They found that 83% obtained an optimal response (PGA $<$ 2) without additional side effects, confirming that a flexible treatment may represent a good option for dermatologists. Alongside these studies regarding primarily a unique cycle of re-treatment, a retrospective observational study seems to show the efficacy of multiple courses of re-treatment.[31] The authors also stated that no case of relapse (defined as a loss of response higher than PASI50 improvement) after therapy was interrupted, or conversion of the morphology of psoriasis, or any other severe adverse events were observed.

The reported data show that, although a continuous long-term treatment permits the attainment of a better clinical response, in some cases an interrupted treatment may be an efficacious alternative and a cycle of re-treatment gives similar results to the former.

## Switching to Etanercept from Another Biological Treatment

Several biological treatments are approved in the treatment of psoriasis; in particular, two other TNF alpha antagonists may be used: adalimumab and infliximab. Although they share the same target as etanercept, TNF alpha blocking drugs have different chemical structures and different mechanisms of action. Therefore, if a patient experiences a lack of response to any drug of this class, this does not predict a lack of response to another drug. This has been shown particularly in rheumatological diseases,[32,33] but also applies to psoriasis. Initially, Pitarch et al evaluated retrospectively the efficacy and safety of etanercept (25 mg BIW) in 8 patients affected by moderate-to-severe plaque psoriasis in which previous treatment with infliximab had been suspended due to lack of efficacy or for other reasons.[34] The mean period of time between the last dose of infliximab and the first dose of etanercept was 71.9 days. They found that 5 patients achieved PASI75 after 12 weeks of treatment with etanercept; in particular 4 out of the 6 patients who had suspended infliximab due to unresponsiveness, responded to

treatment with etanercept while the other 2 patients were still unresponsive. More recently, Mazzotta et al reviewed retrospectively the data of their 124 patients in treatment with etanercept.[35] They found that there was no statistically significant difference, at any timepoint, in the mean PASI score improvement between the patients who had previously received other biologics (26 patients) and those who had not (98 patients). Similar data were recorded when considering also the safety profile. These findings therefore suggest that etanercept may be a useful therapeutic choice for those patients already treated unsuccessfully with another TNF alpha antagonist. Moreover, consecutive administration of several TNF alpha antagonists does not seem to be associated with a greater incidence of adverse effects.

In addition, Antoniou et al published the data of a retrospective study[36] aimed at evaluating the effectiveness and safety of treatment with etanercept in patients previously treated with efalizumab. Efalizumab is a recombinant, humanized monoclonal antibody that targets the alpha-subunit (CD11a) of the leukocyte function-associated antigen-1 (LFA-1). Efalizumab has recently been commercially withdrawn in Europe as it was shown to induce a progressive multifocal leukoencephalopathy. The authors found that 57% of patients achieved a PASI75 improvement after 24 weeks from the start of etanercept. However, they also found that in these patients a bridge-therapy combining etanercept with CsA or MTX is a more effective approach, particularly in those experiencing a rebound phenomenon after suspension of efalizumab.

## Combined Treatment with Etanercept

Various therapies offering good disease control are available to treat psoriasis. However, different treatments, combined or used in rotation, are needed for refractory patients and for those who do not tolerate high-dosage or long-term therapy with a number of drugs. Etanercept, as well other biologic therapies, has been used in association with various traditional treatments.

Extensive data exist in literature regarding the association between etanercept and MTX. MTX has long been used as a traditional therapy for psoriasis, its major limit being the risk of cumulative toxicity. Zachariae et al conducted a randomized, open-label, 24-week study that evaluated the effect of adding etanercept in cases where MTX had failed or had had insufficient effect.[37] Patients receiving etanercept were randomized to taper and discontinue MTX (28 patients) or to continue MTX (31 patients). Safety profiles were similar between the two groups, while the proportion of patients judged responsive to the therapy according to the PGA and PASI score at week 24 was higher in the group of patients which continued MTX treatment in association with etanercept. The evidence of the efficacy and safety of this combined treatment is also confirmed by various case series in high-need psoriatic patients[38] and in the EASE study.[39] This latter was a multi-centre, randomized, open-label trial which matched continuous and intermittent etanercept therapy in psoriatic patients. In this study, subjects who had been on a stable dose of MTX inferior to 20 mg weekly were permitted to continue their treatment when enrolled. This combined therapy was found to be more effective in achieving an improvement in the cutaneous disease than treatment with etanercept alone. No significant side effects were recorded in either course of treatment. Etanercept also permitted the tapering and discontinuation of MTX without any risk of exacerbating psoriasis, as was also found by Yamauchi et al.[40] Moreover, large-scale studies involving predominantly rheumatoid arthritis patients confirmed that MTX and etanercept, in this combined regimen, have a synergistic effect, while their cumulative safety profile is comparable with that of either single therapeutic agent when used in monotherapy.[41–43] Few studies have assessed the role of a combined regimen with CsA and etanercept. The first study, excluding some reports regarding the efficacy of etanercept in patients tapering and then suspending CsA due to side effects, was by D'Angelo et al.[44] They evaluated the efficacy of adding CsA 3.0 mg/kg daily in 11 patients being treated with etanercept for psoriatic arthritis who had failed to obtain an effective response to the concomitant skin disease. After 24 weeks of this combined therapy, 9 patients obtained a meaningful improvement (PASI75) in the psoriasis, while 2 patients stopped CsA as a result of ongoing side effects (raised serum creatinine levels and worsening of hypertension). More recently, a combination therapy with low-dose

cyclosporin (200 mg daily) and etanercept (50 mg QW) was evaluated in 7 patients with refractory psoriasis.[45] Each patient improved rapidly (94.9% PASI reduction in 6.85 weeks) and a maintenance therapy with lower dosage (etanercept 25–50 mg monthly and cyclosporin 50–100 mg daily) permitted this result to be maintained for a long period (56.5 weeks). However, wider randomised and controlled trials are needed to really assess the efficacy and safety of this combined regimen.

Another drug used in association with etanercept is acitretin. This is a systemic retinoid that acts on the keratinocyte proliferation and differentiation without any immunosuppressive effect. This mechanism of action makes it theoretically the ideal drug to associate with etanercept. After a reported case series,[46] Gisondi et al conducted a 24-week, randomized, controlled, investigator-blinded trial with 60 patients affected by moderate to severe psoriasis to evaluate the efficacy and safety of this combined therapy.[47] They divided the enrolled patients into 3 groups receiving etanercept 25 mg BIW subcutaneously, oral acitretin 0.4 mg/kg daily or etanercept 25 mg QW plus acitretin 0.4 mg/kg daily. They then found that the combined regimen was as effective as the monotherapy with etanercept 25 mg BIW (patients achieving PASI75 at week 24, 44% versus 45%) thus allowing them to obtain the same clinical result with reduced costs due to the halved etanercept dosages. Moreover, the safety profiles of the three groups were similar.

Despite the fact that some theoretical doubts about its safety have been widely expressed,[48] a combined treatment regimen including NB-UVB and etanercept has been also assessed. Kircik and co-workers, in their single-arm, open-label study found that 84.9% of 86 patients treated with etanercept 50 mg BIW plus NB-UVB (3 times weekly) for 12 weeks achieved PASI75.[49] Since groups receiving etanercept and NB-UVB monotherapy were not included in the study, improvements were compared with data of literature, which demonstrated that either treatment on its own is associated with a lower efficacy. No meaningful adverse events were described. Moreover, Wolf and colleagues showed that NB-UVB significantly accelerates and improves the clearance of psoriatic lesions in slow responders to etanercept monotherapy. Five patients with moderate-to-severe psoriasis who did not reach PASI75 after 6 weeks on etanercept 50 mg BIW underwent 311 nm UVB phototherapy on a randomly selected body half during treatment with etanercept at the same dosage for a further 6 weeks. The irradiated body halves showed a better response to treatment, as demonstrated by an 89% overall reduction of the baseline PASI score (vs. 68% in non-irradiated areas) at week 12.[50] Although the data about safety in these studies were reassuring, the doubts about long-term safety in these patients persist. In fact, several case reports have highlighted the potential risk of skin cancer in patients receiving anti-TNF-α agents, and extensive observational studies, particularly of patients with rheumatoid arthritis, have yielded conflicting data.[51,52] In addition, experimental studies suggest that skin cancer is a potential long-term side effect of NB-UVB phototherapy, although this hypothesis is not fully confirmed by clinical data.[53] Thus, long-term follow-up of these patients is warranted, to promptly detect any pre-cancerous or neoplastic skin lesions that might arise as a consequence of the mutagenic (presumably UVB-related) and immunosuppressive effects of the treatment. For this reason, in a regimen combining phototherapy with any TNF-α blocker, UV radiation should be administered in as short a course as possible, to minimise the potential risk of the development of cutaneous malignancies.

## Safety Concerns

The role of etanercept in blocking a pleotropic molecule, TNF alpha, justifies its efficacy, but raises doubts as to the safety of this drug. Indeed, while its efficacy is evident and easy to outline, the risks of treatment continue to be defined. Of the potential side effects, those which are acute and chronic must be distinguished. The short-term safety of etanercept has been well established by several clinical trials in psoriasis, as well as in other autoimmune diseases. A similar percentage of subjects experiencing acute adverse events was found among patients receiving etanercept or a placebo in clinical trials. However, injection site reactions seemed to occur more frequently in patients receiving the treatment, even though this was rarely the cause of

therapy withdrawal.[12] On rare occasions, a slightly higher rate of headache and "flu syndrome" has also been recorded.[12] On the other hand, long-term safety is more difficult to assess. The large majority of the data concerning this argument comes from national rheumatological registries. Although these provide larger numbers of patients and longer periods of observation than clinical trials, they may contain a lot of bias. In fact, they are not as selective and controlled as trials, and they involve a population with a higher level of illness, with concurrent diseases and therapies. Moreover, the data deriving from these rheumatological databases may not be transferable to the psoriatic population. In addition, the epidemiological data obtained may also be influenced by the disease target of the treatment. Unfortunately, data on side effects deriving from psoriasis registries have not yet been reported.

That being stated, infection is the most common category of side effect experienced by patients treated with Etanercept, maybe due to the role of TNF alpha in the immune response to bacterial and viral infections.[54] In the previously cited study reporting data with the longest period of follow-up (4.5 years) of 506 patients treated with Etanercept and enrolled in previous trials and open-label extensions, the exposure-adjusted rates for all infectious and serious infectious adverse effects at study completion were 96.9 and 0.9 events per 100 patient-years respectively.[24] The organs most commonly involved were the nasopharynx and the upper respiratory tract and the incidence of serious infections was 12, including, in particular, septic shock, bronchitis, cellulites and viral meningitis. Special consideration is needed regarding tuberculosis; today, it is, in fact, well accepted that anti-TNF therapy can reactivate latent tuberculosis.[55] However, several authors have found that this risk is lower in patients treated with etanercept than in those treated with other anti-TNF alpha agents:[56,57] a study by Dixon et al in particular, found that TB reactivation occurs 4.9 and 3.5 times more frequently respectively in infliximab and adalimumab treated patients.[58]

Another interesting subject is the safety of etanercept in patients with a concomitant chronic viral infection. In particular, it seems to be safe in patients infected with HIV and HCV.[59] In this latter case, several case reports have showed that this drug does not compound the liver damage, as can be seen from monitoring viral load and serum transaminase levels[60,61] and, in the case of two patients, from liver histopathology.[62] On the other hand, HBV infection does seem to be a relative contraindication to anti TNF therapy.[59]

Significant concern also regards the long-term risk of malignancies in these patients. While the incidence of solid tumors does not seem to be increased, several case reports have highlighted the potential risk of skin cancer in patients receiving anti-TNF-α agents, and large observational studies, particularly of patients with rheumatoid arthritis, have yielded conflicting data.[63,64] Moreover, there has been concern over the risk of lymphoma with use of these agents as a result of their immunosuppressive properties. Current data are controversial, and an increased risk of lymphoma in these patients cannot be ruled out, although a causal relationship between biologics and lymphoma has not been established. However a short-term treatment appears certainly to be safe.[65]

Etanercept should be avoided in patients with a personal history of any central nervous system demyelinating disorder and used with caution in patients with a family history of these disorders, since demyelinating diseases are rare adverse events of anti-TNF-alpha therapy. Antinuclear antibodies and anti-DNA antibodies develop in patients treated with anti-TNF alpha agents,[66] even though cases of drug induced lupus erythematous are very rare,[67,68] particularly in etanercept treated patients. A few other cutaneous side effects have been reported, including leukocytoclastic vasculitis, lichenoid reactions and Stevens-Johnson syndrome.[69] Particularly intriguing are cases of induction or exacerbation of psoriasis during treatment with Etanercept as well with other TNF inhibitors, given for psoriasis or other approved autoimmune diseases. Palmoplantar pustular psoriasis was the most frequently observed form.[70] Finally, Etanercept should be avoided in patients with moderate-to-severe congestive heart failure (CHF) (New York Heart Association [NYHA] class III/IV), and used with caution in those with mild CHF (NYHA class I/II).[71] The reason for this is that cases of new onset or worsening of previously diagnosed

heart failure have emerged from post-marketing studies[72] in patients treated with TNF inhibitors. However, while clinical trials with etanercept in the treatment of III-IV CHF were disappointing,[73,74] data from a national German Arthritis register evaluating the efficacy of TNF alpha blockers in AR patients, seem to suggest a beneficial effect of etanercept in patient with CHF.[75]

## Pharmaeconomy

As a consequence of the expense of biological drugs, several studies have been done to estimate the cost-effectiveness of these therapies. A German group evaluated this aspect of treatment with etanercept in comparison to non-systemic therapy.[76] They performed a cost-utility analysis using as an endpoint costs per quality-adjusted life year gained. Data on efficacy and safety over a 10 year course were taken from previous clinical trials. The incremental cost-effectiveness ratio for etanercept correlated with disease severity being 45,491€, 32,058€ and 18,154€ respectively, in patients with a PASI score >10, >15 or >20. Thus, the authors concluded that, according to internationally accepted levels of cost-effectiveness thresholds, the intermittent treatment of moderate to severe plaque-type psoriasis with etanercept is a cost-effective measure within the German healthcare system. Wu et al adjusted the data on the annual cost of etanercept taking into consideration the dosage escalation which happens in a real-world setting.[77] They found that among patients continuously treated for 1 year, an additional annual cost of 8440$ and 9313$ for 100 and 50 mg weekly dosage respectively has to be considered with respect to the expected costs imputed from label indications. Lloyd et al showed that, although etanercept 50 BIW was more costly than etanercept 25 mg BIW, the cost-effectiveness of the former was more attractive for patients with a severe disease (PASI > 20) or with a poor quality of life (DLQI > 20) at baseline.[78]

Nelson et al matched the cost-effectiveness of the biologic agents approved for psoriasis treatment taking into account the cost per patient achieving a minimally important difference in DLQI and per patient achieving PASI75, assessed over a 12 week period.[79] Considering efficacy through DLQI, they found that Etanercept 25 QW was the most cost-effective agent, whilst when administered BIW it was less cost-effective than infliximab (3 mg/kg) and adalimumab (40 mg every other week). Moreover, Etanercept 50 mg BW was the lowest cost-effective regimen. Instead, when efficacy was evaluated through PASI75 improvement, Etanercept 25 mg BIW, 50 mg BIW and 25 mg QW were respectively the three least cost-effective treatments. However, the major limitation of this study was represented by the limited time horizon. In addition, the data utilized were derived from an idealized randomized control study that may not correspond to the outpatient setting. However, similar findings were reported by other authors.[80–82] In particular, Sizto et al determined the cost-effectiveness of every systemic treatment for psoriasis, taking into consideration also data regarding traditional drugs, MTX and CsA.[83] The authors found that traditional therapies were cost effective, but they did not consider the possible related adverse events and so they did not take into account the required costs in monitoring for toxicities. In fact, Fonia et al subsequently showed that, although total healthcare costs associated with biologic therapy are significantly higher than with traditional systemic therapy, they are offset by substantial reductions in the number and length of hospital admissions and use of photo- and systemic therapy. In addition, they result in significantly improved patient outcomes.[84] These findings were also confirmed when cost-effectiveness data also took into account treatment failures.[85] Finally, a longitudinal cohort study of psoriatic patients enrolled in North Carolina Medicaid showed that total health care costs did not differ significantly in the post-biologics period when compared with the previous years.[86]

## Conclusions

In conclusion, our study confirmed the emerging therapeutic value of etanercept in the treatment of psoriasis. Since its approval, several randomised clinical trials have demonstrated its efficacy in the short and long-term, both in a continuous and interrupted course of therapy. Data deriving from these studies have also suggested an acceptable safety profile, as found in studies conducted about its use in other autoimmune diseases. In addition, etanercept

seems to be efficacious and safe when administered in a combined treatment with other traditional medications as well as after switching from another biological drug. Indeed, despite its high costs it does seem to be cost-effective.

## Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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