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REVIEW

# Long-term safety and efficacy of etanercept in the treatment of ankylosing spondylitis

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**Abstract:** To date, anti-tumor necrosis factor alfa (anti-TNF-α) therapy is the only alternative to nonsteroidal anti-inflammatory drugs for the treatment of ankylosing spondylitis. Etanercept is a soluble TNF receptor, with a mode of action and pharmacokinetics different to those of antibodies and distinctive efficacy and safety. Etanercept has demonstrated efficacy in the treatment of ankylosing spondylitis, with or without radiographic sacroiliitis, and other manifestations of the disease, including peripheral arthritis, enthesitis, and psoriasis. Etanercept is not efficacious in inflammatory bowel disease, and its efficacy in the treatment of uveitis appears to be lower than that of other anti-TNF drugs. Studies of etanercept confirmed regression of bone edema on magnetic resonance imaging of the spine and sacroiliac joint, but failed to reduce radiographic progression, as do the other anti-TNF drugs. It seems that a proportion of patients remain in disease remission when the etanercept dose is reduced or administration intervals are extended. Etanercept is generally well tolerated with an acceptable safety profile in the treatment of ankylosing spondylitis. The most common adverse effect of etanercept treatment is injection site reactions, which are generally self-limiting. Reactivation of tuberculosis, reactivation of hepatitis B virus infection, congestive heart failure, demyelinating neurologic disorders, hematologic disorders like aplastic anemia and pancytopenia, vasculitis, immunogenicity, and exacerbation or induction of psoriasis are class effects of all the anti-TNF drugs, and have been seen in patients with ankylosing spondylitis. However, etanercept is less likely to induce reactivation of tuberculosis than the other anti-TNF drugs and it has been suggested that etanercept might be less immunogenic, especially in ankylosing spondylitis. Acute uveitis, Crohn's disease, and sarcoidosis are other adverse events that have been rarely associated with etanercept therapy in patients with ankylosing spondylitis.

**Keywords:** ankylosing spondylitis, etanercept, spondyloarthritis, efficacy, safety

## Introduction

Spondyloarthritis refers to a heterogeneous group of diseases that share clinical, pathogenic, and hereditary features, and include ankylosing spondylitis (AS) and psoriatic arthritis. The spondyloarthritides are characterized by chronic inflammation of the enthesis with a tendency to bone ankylosis. The most frequent clinical features are sacroiliitis, enthesitis, iritis, oligoarthritis, psoriasis, and inflammatory bowel disease.[1]

The prevalence of spondyloarthropathy is estimated to be between 0.1% and 2.5%, although figures vary from one study to another. The reported incidence ranges from 0.3 to 7.3/100,000 inhabitants per year.[2] The impact on quality of life can be very negative, given that pain and functional disability affect patients both physically and psychologically.

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Nonsteroidal anti-inflammatory drugs and physical exercise have been the cornerstone of treatment for spondyloarthritis, but are not effective in some cases. Other disease-modifying antirheumatic drugs (DMARDs) like sulfasalazine, methotrexate, or leflunomide, are recommended for treating peripheral arthritis or extra-articular features. However, in cases of exclusive spinal involvement that do not respond to nonsteroidal anti-inflammatory drugs, the only option to date is to use anti-tumor necrosis factor (TNF) drugs. Since the advent of anti-TNF drugs, the symptoms of spondyloarthritis have improved dramatically. Further, their use has been linked to the clearing of active lesions on magnetic resonance imaging (MRI), such as bone edema, but the studies published to date have not demonstrated prevention of structural damage.[3]

The primary target of treatment is remission of the disease and, when that fails, to minimize inflammatory activity, to improve the signs and symptoms of spondyloarthritis, and to prevent structural damage and functional disability, thus safeguarding the patient's quality of life. Therefore, persistence of activity indicates the need for a change of treatment.

The Assessment of Spondyloarthritis International Society (ASAS) recommends use of anti-TNF in patients diagnosed with AS or spondyloarthritis if they have active disease and have not improved with conventional treatment.[4] Currently, there are four anti-TNF agents approved for spondyloarthritis, including three monoclonal antibodies, ie, infliximab, adalimumab, and golimumab, and a soluble TNF receptor, etanercept. All four have efficacy demonstrated in randomized clinical trials, with significant superiority over placebo and about 60% of patients reaching an ASAS 20 response versus 20% of patients assigned to placebo.

Etanercept is composed of two recombinant forms of the human TNF receptor P75 fused to an Fc portion of human immunoglobulin G1, and is administered subcutaneously 50 mg a week or 25 mg twice a week. It has a differences regarding way of action and pharmacokinetics, what implies differences with antibodies in effectiveness and safety.

In this paper, we review the efficacy and safety of etanercept in the treatment of AS, and how it differs from the other anti-TNF drugs reported in the literature.

# Efficacy of etanercept in ankylosing spondylitis

## Efficacy outcome measures used in the studies

Disease activity in patients with AS has been evaluated using the Bath Ankylosing Spondylitis Disease Activity Index[5] (BASDAI), physical function using the Bath Ankylosing Spondylitis Functional Index[6] (BASFI), and mobility by the Bath Ankylosing Spondylitis Metrology Index[7] (BASMI).

In 2001, the ASAS developed outcome measures recommended for use in trials of symptom-modifying therapy.[8] The ASAS 20 improvement criteria summarize changes in the domains of physical function, pain, patient global assessment, and inflammation. A positive response is defined as a 20% or greater improvement and a net improvement of one unit on a 10-unit scale in each of three domains, with no worsening in the fourth. An ASAS 40 response is defined as ≥40% improvement of at least two units in each of three domains, with no worsening in the fourth. ASAS partial remission is defined as a score below two units in each domain, and ASAS 5/6 is defined as 20% improvement in five of six domains, adding C-reactive protein and lateral vertebral flexion.

More recently, the ASAS association has validated the Ankylosing Spondylitis Disease Activity Score,[9] that includes C-reactive protein levels in addition to some of the BASDAI questions and is a highly discriminatory instrument for assessing disease activity in AS.

## Efficacy in ankylosing spondylitis

The efficacy of etanercept in AS has been assessed in several randomized clinical trials (Table 1). The first to evaluate the efficacy of etanercept in AS was published in 2002, with 40 active AS patients randomly assigned to receive etanercept 25 mg twice weekly or placebo for 4 months.[10] The intention-to-treat analysis revealed an ASAS 20 rate of 80% in the etanercept group versus 30% in the placebo group ($P = 0.004$). Significant improvement was achieved in four of the five measures of ASAS 20. The treatment arm also showed significantly greater improvement in many of the secondary outcome measures (physician's global assessment of disease activity, chest expansion, erythrocyte sedimentation rate, and C-reactive protein level). Patients in the placebo group were treated with etanercept in a 6-month, open-label extension of the trial, with a rapid response and no statistically significant differences in efficacy from patients treated with etanercept throughout the entire 10-month period.[11]

In June 2003, a multicenter randomized clinical trial including 30 patients with active AS was published.[12] In the first phase of the study, patients were randomized to receive either etanercept 25 mg twice weekly (n = 14) or placebo (n = 16) for 6 weeks. Nonsteroidal anti-inflammatory drugs were permitted, but steroids and DMARDs had to be stopped prior to the study. The primary outcome parameter (>50% improvement on BASDAI) was achieved by 57% of the

**Table 1** Main randomized clinical trials analyzing the efficacy of etanercept in ankylosing spondyloarthritis

| Reference | Year | Type | n | Duration (weeks) | Endpoints | *P* |
|---|---|---|---|---|---|---|
| Gorman et al[10] | 2002 | RCT | 20/20 | 16 | ASAS 20 | 0.004 |
| Davis et al[11] | | OLE | 17 | 40 | | |
| Brandt et al[12,13] | 2003 | RCT | 14/16 | 6 | BASDAI 50, ASAS 20, BASDAI, BASFI, BASMI | 0.004 |
| | | OLE | 23 | 54 | | |
| Davis et al[14,15] | 2003 | RCT | 138/139 | 24 | ASAS 20 | 0.0001 |
| | | OLE | 128* | 192 | | |
| Calin et al[16] | 2004 | RCT | 45/39 | 12 | ASAS 20, 40, 5/6, BASDAI | 0.001 |
| Dijkmans et al[17] | | OLE | 43 | 96 | | |
| van der Heijde et al[18] | 2006 | RCT | 305/51 | 12 | ASAS 20, 40, 5/6 | 0.001 |
| Braun et al[19] | 2007 | RCT | 305/51 | 12 | BASFI, EuroQOL-5D, SF-36 | 0.001 |
| Braun et al[20] | 2011 | RCT | 379/187 | 16 | ASAS 20, 40, 5/6, BASDAI, BASFI, BASMI | 0.0001 |
| Li et al[21] | 2013 | MET | 1,570 | - | ASAS 20, 40, 5/6, partial remission, BASFI, BASDAI, BASMI | 0.00001 |

**Note:** *Includes only patients receiving ETN from the beginning of the study.
**Abbreviations:** ASAS, Assessment of Spondyloarthritis International Society; ETN, etanercept; MET, meta-analysis; OLE, open-label extensions; RCT, randomized clinical trial; BASFI, Ankylosing Spondylitis Functional Index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index.

etanercept group versus 6% of the placebo group ($P = 0.004$). An ASAS 20 response was achieved by 78.6% versus 25% of patients, respectively. Similarly, pain, physical function, mobility, quality of life, and scores on BASDAI, BASFI, and BASMI improved significantly. In the second phase of the study, both groups (placebo and etanercept) were treated with etanercept for 12 weeks, and 56% of patients in the placebo group achieved a >50% improvement in BASDAI score. After 12 weeks of treatment, all patients discontinued etanercept, and 75% experienced a relapse in a mean of 27 weeks. These patients were eligible to restart etanercept in a 54-week, open-label extension trial.[13] The intention-to-treat analysis showed that 57.7% of patients achieved a 50% improvement in the BASDAI, and 73.1% were responders using the ASAS 20 criteria. This confirms that readministration of etanercept is efficacious and safe in AS patients.

Another multicenter randomized clinical trial in 2003 assessed the efficacy of etanercept in 277 AS patients.[14] In the first 24-week, double-blind trial, patients were randomized to receive etanercept 25 mg or placebo twice weekly. The primary outcome measure, ASAS 20, was achieved by 59% of patients in the active treatment group and by 28% of patients in the placebo group at week 12, and by 57% and 22% patients, respectively, at week 24, with a statistically significant difference between the groups. ASAS 50 and 70 responses were achieved in 40% and 20% of etanercept patients, respectively. In an open-label extension of this study, 257 patients received etanercept for 168 weeks.[15] The patients who had received etanercept in the double-blind trial had a sustained response, with 71% achieving an ASAS 20 at week 96 and 81% at week 192. Patients who switched to etanercept in the open-label extension had similar responses, with 70% attaining an ASAS 20 at week 24, 78% at week 72, and 82% at week 168.

In 2004, another multicenter randomized clinical trial was performed in Europe, with 45 patients randomly assigned to etanercept 25 mg and 39 to placebo twice weekly for 12 weeks.[16] Significantly more patients were ASAS 20 responders in the etanercept group (60% versus 23%, respectively). ASAS 50 and ASAS 70 responses were achieved by 49% and 24% of patients in the etanercept group, respectively. Simultaneous significant improvement of functional status and metrology were observed. A 96-week, open-label extension of this study with 81 patients confirmed the improvement, with 83% of ASAS 20 responders in the etanercept/etanercept group and 74% in the placebo/etanercept group.[17]

In 2006, a 12-week randomized clinical trial compared the efficacy of etanercept 50 mg once weekly with that of etanercept 25 mg twice weekly and placebo in 365 patients with AS.[18] Similar discontinuation rates were found between the etanercept groups. ASAS 20 response rates were higher in patients on etanercept compared with those on placebo (74.2%, 71.3%, and 37.3%, respectively, $P = 0.001$). Similar results were found when analyzing ASAS 5/6, ASAS 40, and other measures of disease activity. The incidence of adverse events was similar between the three groups. The same doses were compared further in a 12-week randomized clinical trial that assessed patient-reported outcomes in 356 AS patients.[19] Treatment with etanercept 50 mg once weekly or 25 mg twice weekly significantly improved quality of life and functional status compared with placebo. These studies

indicate that both doses of etanercept have comparable levels of efficacy in AS.

In 2011, ASCEND (an open-label, multicentre, supplementary extension study of etanercept in subjects with ankylosing spondylitis) compared the efficacy of etanercept and sulfasalazine in 566 biologic-naïve AS patients.[20] Because the patients included had to be candidates for treatment with sulfasalazine, most had peripheral arthritis (70% in the etanercept group and 74% in the sulfasalazine group), and some had already tried DMARDs (28% in both groups). Patients were randomized to receive etanercept 50 mg once weekly or sulfasalazine (maximum 3 g/day) for 16 weeks. The proportion of ASAS 20 responders was significantly greater in the etanercept group as compared with the sulfasalazine group (76% versus 53%, $P < 0.0001$).

Finally, a recent meta-analysis that included 1,570 participants has investigated the efficacy of etanercept in Caucasian versus Chinese populations.[21] Nine of the 14 randomized clinical trials included the ASAS 20 criteria, which was achieved by 72% of patients in the etanercept group versus 28% in the placebo group ($P < 0.00001$), with no significant heterogeneity between the studies. Similar results were found for ASAS 40, ASAS 5/6, ASAS partial remission, BASFI, BASDAI, BASMI, and patient global assessment. In addition, etanercept was effective in relieving total back pain, nocturnal pain, and morning stiffness, although no difference was found in improving chest expansion, occiput-to-wall distance, and tender or swollen joint scores. Further, they found that, compared with the Chinese population, the Caucasian population showed higher rates of ASASA 40 and ASAS partial remission, and a higher incidence of treatment-emergent adverse events.[21]

## Comparative efficacy between anti-TNF therapies

The efficacy of the four anti-TNF drugs available for AS has not been directly compared in randomized clinical trials. Indirect comparisons are limited and do not show a significant difference in effectiveness between them.[22] Survival rates extracted from national registries have been used as a surrogate marker of efficacy, but controversial results have been reported. Data from the Austrian national register show better 2-year survival rates with etanercept than with adalimumab or infliximab,[23] while the Danish national register shows no statistically significant differences between the three drugs.[24] Overall drug survival for patients with rheumatoid arthritis, psoriatic arthritis, or AS was better for etanercept than for infliximab or adalimumab in the Norwegian registry,[25] but this difference no longer exists when analyzing only first anti-TNF treatments. In the Czech registry,[26] there were no differences in survival rates between the anti-TNF agents, although the difference between etanercept and infliximab was near statistical significance ($P = 0.057$). In addition, they found a higher proportion of patients with BASDAI $< 4$ in the etanercept group than in the infliximab group.

## Efficacy as second-line anti-TNF therapy

Although biologic therapy can provide rapid improvement in AS symptoms, some patients may not respond to their first anti-TNF drug and other patients may worsen over time. This observation, along with treatment withdrawal due to adverse events, makes switching between anti-TNF drugs common in everyday clinical practice. Efficacy on switching to a second anti-TNF drug has been evaluated in observational studies, with good response rates.[27]

Few studies have assessed the efficacy of etanercept in patients who have failed to respond to previous biologic therapy. Switching from infliximab to etanercept has been evaluated in two observational studies, and reported good clinical response rates.[28,29]

## Efficacy in axial spondyloarthritis without radiographically defined sacroiliitis

Recently, new ASAS classification criteria for axial spondyloarthritis have been published, covering both patients with and without radiographic sacroiliitis.[30] ABILITY (A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects With Axial Spondyloarthritis) demonstrated the efficacy of adalimumab in reducing disease activity in these patients,[31] and before these criteria were ready infliximab also demonstrated good clinical efficacy in AS patients without radiographic sacroiliitis.[32]

The efficacy of etanercept in patients with preradiographic AS that fulfilled ASAS axial criteria was assessed in the ESTHER (effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body magnetic resonance imaging) trial comparing etanercept with sulfasalazine.[33] At week 48, reduction of edema in the sacroiliac joint on whole-body MRI was significantly greater in the etanercept group than in the sulfasalazine group. In addition, there was a reduction in most clinical variables, and 50% of patients in the etanercept group reached clinical remission.

Another randomized clinical trial with ASAS axial patients, that has not yet been published, found a better ASAS 40 response in the etanercept group versus placebo (32.4% versus 15.7%, $P < 0.01$).[34]

## Efficacy in severe long-standing disease

The effect of etanercept in long-standing active AS was analyzed in a multicenter, 12-week, randomized clinical trial with 82 anti-TNF-naïve patients. The patients had to have radiologic intervertebral bridges or spine fusion and a BASDAI > 4. This study reported greater improvement on BASDAI (area under the curve between baseline and week 12) in the etanercept group (−19.8 ± 16.5 versus −11.0 ± 16.4, $P = 0.019$).[35] In a 12-week, open-label extension of the trial, a significant decrease in nonsteroidal anti-inflammatory drug intake was found in the etanercept group.[36]

## Efficacy in hip lesions, peripheral joints, and extra-articular manifestations

As previously noted, the most frequent clinical features of AS are sacroiliitis, enthesitis, iritis, oligoarthritis, psoriasis, and inflammatory bowel disease. The efficacy of etanercept in enthesitis was demonstrated by the ESTHER trial in patients with preradiographic AS on the basis of reduction of bone marrow edema on MRI at 27 enthesitic sites, including facet joints, costovertebral joints, and spinous processes.[33] Etanercept is efficacious in the treatment of psoriasis[37] and psoriatic arthritis,[38,39] but no benefit was observed in the treatment of inflammatory bowel disease.[40] In a recent randomized clinical trial, etanercept was more effective than sulfasalazine in reducing the number of swollen joints in AS patients.[41] In one observational study, etanercept was able to alleviate hip symptoms in patients who had not responded to conventional therapy.[42] The efficacy of etanercept in preventing flare-up of anterior uveitis is reviewed elsewhere in this article.

## Reduction of inflammation on MRI and radiographic progression

Reduction of inflammation in AS patients by etanercept is also confirmed as regression of bone edema assessed by spinal MRI.[43,44] Nevertheless, radiographic progression has been analyzed in several trials with controversial results. Most of the studies that evaluated radiographic progression used the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) method.[45] In a previously discussed trial, most patients had no radiographic progression using the mSASSS method at 60 weeks.[17] However, in another 2-year randomized clinical trial, no differences in radiographic progression were found when comparing etanercept-treated patients with an anti-TNF-naïve cohort.[3] Similarly negative findings were obtained with infliximab[46] and adalimumab,[47] leading to the suggestion that structural progression in AS is independent of TNF.

## High-dose efficacy

In 2011, a 12-week, randomized clinical trial evaluated the efficacy of etanercept 50 mg once weekly versus twice weekly in 108 AS patients who had previously failed standard therapies. No significant differences were found in any efficacy endpoint between the treatment groups.[48]

## Dose-tapering, extending intervals, or drug discontinuation

Biologic drugs are an expensive therapy and a heavy economic burden for health care systems in many countries. Dose-tapering, extending intervals of administration, and drug discontinuation in patients in clinical remission are currently common practices with biologic therapy since they serve to curb health care costs. The efficacy of these practices has been assessed in several open-label studies.

Dose-tapering and interruption of etanercept was analyzed in a prospective uncontrolled trial with active AS biologic-naïve Korean patients.[49] Treatment with etanercept 50 mg once weekly was given for 3 months, and the dose was then tapered to 25 mg once a week for 6 months, and finally discontinued. In the first 3 months, four (14.8%) of 27 patients dropped out because of lack of response, and one patient relapsed and five patients were lost to follow-up on 25 mg maintenance therapy. After discontinuation, 67% of patients relapsed within 9 weeks.

In the aforementioned ESTHER trial, 8% of patients with axial spondyloarthritis treated with etanercept for one year remained in permanent drug-free remission during the year versus 3% of patients in the sulfasalazine group, but this difference was not statistically significant.[50] The efficacy of readministration of etanercept after treatment discontinuation was assessed in a previously discussed study with good results.[13] Extending dosing intervals was assessed by another retrospective Korean analysis of 109 AS patients treated with etanercept.[51] Patients started etanercept 25 mg twice weekly and the dosing interval gradually increased to 4.7 ± 2.1 days at 3 months, 8.5 ± 4.9 days at 9 months, 9.9 ± 5.8 days at 15 months, and 12.1 ± 7.0 days at 21 months. BASDAI decreased from 8.5 to 0.6 at 21 months.

A very recent randomized prospective study evaluated the proportion of patients with AS maintaining clinical remission after extending etanercept 50 mg administration to every

other week.[52] Patients were randomized 1:1 to a standard once-weekly or an extended dose. At the end of an average follow-up of 21 weeks, the rate of remission maintained was 90% and 86%, respectively, with no statistically significant difference between the two regimens.

Finally, in an observational study in routine clinical practice, the etanercept dose was reduced in 16 AS patients in clinical remission, defined as BASDAI $< 4$ and normal C-reactive protein levels.[53] Different patterns of dose reduction were used: 25 mg weekly in four patients (25%), 25 mg every 10 days in one patient (6.3%), 25 mg every other week in two patients, 50 mg every 8 days in three patients (18.7%), and 50 mg every 10 days in the remaining six patients (37.5%). All patients remained on the low-dose regimen after a mean follow-up of $21 \pm 21$ months.

## Intra-articular etanercept

Promising results were obtained in 16 Chinese AS patients receiving computed tomography-guided intra-articular injections of etanercept 25 mg at 0, 4, and 8 weeks.[54] The long-term efficacy of this new route of administration remains to be demonstrated.

## Work disability

The effectiveness of etanercept in preventing work disability as a result of AS was assessed in a small, double-blind, placebo-controlled, 12-week trial with 40 patients using the Ankylosing Spondylitis Work Instability Scale.[55] Differences between groups were not statistically significant, probably due to the high rate of long-standing disease and the short duration of the study. However, in another study, etanercept showed improvement in work productivity among AS patients, with an increase in the full-time employment rate of 6.8% and a decrease in mean number of sick days to 22 days.[56] Similar results were found with other anti-TNF drugs,[57] so that the effect of these agents on work participation in real life should be examined further in larger population-controlled studies.

# Safety of etanercept in AS

There are some differences between etanercept and other TNF-α blockers in terms of their mechanism of action. Etanercept does not induce apoptosis in some tissues (eg, the gastrointestinal mucosa), while both anti-TNF-α soluble receptor and monoclonal antibodies seem to cause apoptosis in the synovium.[58] In contrast with adalimumab or infliximab, etanercept does not activate complement-dependent cytolysis or antibody-dependent cell-mediated cytotoxicity. In fact, etanercept contains the Fc portion of immunoglobulin G1, but does not fix the complement.[58] The hypothesis of different steric accessibility of the Fc region of etanercept could explain the markedly shorter plasma half-life of etanercept versus monoclonal antibodies.[59] The above-reported findings could explain some differences in the safety profile of etanercept with respect to infliximab and adalimumab.

## Main adverse events

Data on the safety of etanercept in AS come mainly from randomized clinical trials, observational open-label extensions of randomized clinical trials, registers, and case reports. The highest level of evidence is provided by randomized clinical trials and their meta-analyses, but it is important to remember that the populations included in randomized clinical trials are biased by their selection criteria and could be different in actual clinical practice. The main adverse events recorded during randomized clinical trials and two open-label extensions in patients with AS are summarized in Table 2.

In the randomized clinical trials, the rate of adverse events was similar between the treatment and placebo groups, except for injection site reactions, which were more frequent in the etanercept groups.[14,15,17,18] In the open-label

**Table 2** Main adverse events occurring during treatment with etanercept in patients with ankylosing spondyloarthritis in randomized clinical trials and open-label extensions

| Adverse event | AS-RCT[14] | | AS-RCT[18] | | AS-OLE[47] | | AS-OLE[15] | AS-OLE[17] |
|---|---|---|---|---|---|---|---|---|
| | ETN (n = 138) | PL (n = 139) | ETN (n = 151) | PL (n = 51) | ETN TW (n = 54) | ETN OW (n = 54) | ETN (n = 257) | ETN (n = 81) |
| Injection site reactions | 30% | 9% | 23% | 12% | 7% | 8% | 22% | 37% |
| Upper respiratory tract infection | 20% | 12% | 8% | 14% | 5% | 8% | 45% | 53% |
| Headache | 14% | 12% | 4% | 0% | <3% | <3% | 20% | 20% |
| Diarrhea | 8% | 9% | 4% | 0% | <3% | <3% | 18% | 15% |
| Rhinitis | 6% | 6% | <3% | <3% | <3% | <3% | NA | 14% |
| Rash | 8% | 6% | <3% | <3% | <3% | <3% | NA | NA |

**Note:** Adapted with permission from D'Angelo S, Palazzi C, Cantini F, Lubrano E, Marchesoni A, Mathieu A. Etanercept in spondyloarthopathies. Part II: safety and pharmacoeconomic issues. *Clin Exp Rheumatol*. 2011;29:865–870.[89]

**Abbreviations:** AS, ankylosing spondylitis; RCT, randomized clinical trials; OLE, open-label extension; ETN, etanercept; PL, placebo; TW, twice a week; OW, once a week.

extensions,[15,17,47] the number of etanercept discontinuations because of adverse events was very low. Overall, serious adverse events occurred in less than 5% of the patients, and were often unrelated to treatment. These results are similar to those reported for other anti-TNF agents in the treatment of AS. However, further studies are needed to compare safety outcomes, especially with respect to long-term follow-up.[60]

The safety of treatment with etanercept in patients with AS at high doses (100 mg per week) was compared with that of a standard dose (50 mg weekly) in LOADET (A 12-week Randomized, Double-blind, Multicenter Pilot Study to Evaluate the Effect of Etanercept 100 mg and 50 mg Weekly in Subjects With Ankylosing Spondylitis). Adult patients with AS were randomized to receive etanercept 50 mg twice a week or etanercept 50 mg once a week for 12 weeks. They concluded that high-dose etanercept in the treatment of AS for 12 weeks is as safe as the standard dose.[48]

In a recent open-label extension involving 59 AS patients treated with etanercept for 264 weeks (original etanercept group) or 252 weeks (original placebo group), serious infections occurred at a rate of 0.03 events per subject years, while no cases of tuberculosis or opportunistic infections were reported.[61]

## National registry data

Post-marketing surveillance and registers are an interesting source of safety data for unselected patient populations. The Spanish register of biologics, BIOBADASER, included 1,524 patients with spondyloarthritis, of whom 657 had AS.[62] Most of the patients were on infliximab but there was an exposure to etanercept of 134 patient-years for AS. At 3 years, the drug survival rate for all of the three anti-TNF-α agents was 0.76 for AS and 0.73 for psoriatic arthritis, with adverse events responsible for 45.4% of therapy discontinuations. The adverse event incidence rate per 100 patient-years of exposure in all of the 507 patients with spondyloarthritis treated with etanercept was less than 1.0, with the exception of the infection rate, which was only 1.01.

A Norwegian register of DMARD and biologic therapy prescriptions collected 249 patients with AS (among other diseases) receiving a TNF-α antagonist. For 122 of these patients, etanercept was the first biologic.[25] The one-year withdrawal rate for this drug was 24.6%. Adverse events were responsible for 69.2% and 43.6% of discontinuations of anti-TNF-α agents in psoriatic arthritis and AS, respectively.

Our group conducted an observational study comparing the duration of treatment with etanercept with that of the rest of the biologic drugs in our cohort of patients on biologic therapy.[63] We included 205 patients on biologic treatment, 92 patients on treatment with etanercept, 33% of whom had AS. Adverse events as a cause of discontinuation of etanercept occurred in 15 patients (16%).

In conclusion, the data from existing registers seem to indicate that in standard clinical settings of patients with AS, anti-TNF-α agents, and etanercept in particular, are more often responsible for drug discontinuation than in randomized clinical trials but, nevertheless, these molecules have a good safety profile.

Reactivation of tuberculosis, reactivation of hepatitis B virus infection, congestive heart failure, demyelinating neurologic disorders, hematologic disorders like aplastic anemia or pancytopenia, vasculitis, immunogenicity, and exacerbation or induction of psoriasis are class effects seen with all of the TNF-α inhibitors, and have been seen in patients with rheumatoid arthritis and those with spondyloarthritis.[64,65]

## Reactivation of tuberculosis

The number of tuberculosis cases decreased after institution of tuberculosis screening, but the problem has not disappeared completely. Since the screening test may produce false negative results and first infection during etanercept treatment may occur, careful vigilance and repeat screening for tuberculosis has been suggested.[66] It has been confirmed that etanercept is less likely to reactivate tuberculosis than the other TNF-α antagonists.[67,68] In addition, etanercept did not induce any reactivation of tuberculosis in a cohort of 84 patients, including those with AS or psoriatic arthritis or those at high risk for tuberculosis infections (purified protein derivative-positive patients).[69] An interesting point is the relationship between TNF-α blockers and production of interferon-γ. In fact, interferon-γ expression was inhibited by infliximab, but not by etanercept,[70,71] suggesting that the risk of granuloma-dependent infection may reflect an ability to inhibit both TNF-α and (indirectly) interferon-γ.[58]

## Hepatitis B virus, hepatitis C virus, and human immunodeficiency virus

Reactivation of hepatitis B virus, congestive heart failure, and demyelinating diseases are potential adverse events of anti-TNF-α therapy that can occur regardless of the underlying condition. Vasculitis is much more likely to occur in patients with rheumatoid arthritis than in those with spondyloarthritis.[72,73] Treatment with etanercept in the setting of chronic hepatitis C virus infection seems to be safe, but

the relevant data are obtained mainly from studies of patients with rheumatoid arthritis.[64,74]

The safety of etanercept in human immunodeficiency virus (HIV)-positive patients has also been studied. There are published retrospective series of HIV-positive patients with rheumatoid arthritis, spondyloarthritis, or psoriasis treated with anti-TNF drugs (including etanercept). These studies suggest that treatment with anti-TNF-α therapy is a viable alternative for HIV patients without advanced disease but with associated rheumatic diseases refractory to standard therapy.[75,76]

## Immunogenicity

It has been suggested that etanercept might be less immunogenic than the other TNF-α antagonists, especially in AS.[73,77] Immunogenicity, specifically the onset of antibodies against TNF-blocking agents, seems to play an important role in lack of response to treatment with these drugs.[78] Some studies in patients with rheumatoid arthritis have demonstrated that lower etanercept levels were associated with lack of response,[79,80] and antibodies against etanercept, all non-neutralizing, were obtained in less than 2% of the patients.[81] The relationship of clinical response in AS with etanercept levels and the presence of antibodies to etanercept was recently assessed in 53 consecutive patients.[77] All patients with AS had detectable etanercept levels, regardless of whether they were responders or non-responders. In contrast with previous studies of other TNF-blocking agents, no antibodies against etanercept were detected in any of the assays. This study indicates that immunogenicity does not play an important role in explaining the non-response of patients with AS to treatment with etanercept.[77]

## Paradoxical psoriasis

Exacerbation or induction of psoriasis is a paradoxical effect of TNF-α inhibition that is not specific to AS, and has been reported in other diseases.[65] The scientific evidence in this regard suggests that while the anti-TNF-α monoclonal antibodies can induce new-onset psoriasis, etanercept is more likely to cause flare-ups of existing disease.[82]

## Malignancy

The relationship between malignancy and anti-TNF-α drugs is an unresolved concern. In rheumatoid arthritis, some studies did not find an increased incidence of lymphoma or solid cancers in patients taking TNF-α inhibitors, while others did.[83] In a recent systematic review, patients with psoriatic arthritis or psoriasis treated with anti-TNF agents showed increased rates of non-melanoma skin cancer.[84] This risk was increased by treatment with methotrexate, cyclosporine, and phototherapy.

A recent meta-analysis of registries and a systematic review of long-term extension studies did not reveal an increased risk of malignancy in patients with rheumatoid arthritis receiving anti-TNF therapy.[85] The pooled odds ratio for total malignancy and for non-melanoma skin cancers was 0.81 (95% confidence interval [CI] 0.71–0.94) and 0.79 (95% CI 0.62–1.02) in an TNF-antagonist group versus a DMARD group, respectively. Among four long-term studies and four registries, no significant increase in incidence of total malignancy was noted versus the general population. Only an increased risk of non-melanoma skin cancers was found. The presence of many confounding factors, the low rate of malignancies, and the long length of time needed for a cancer to develop complicate the search for an answer to this question. Although the data on malignancy in patients with spondyloarthritis treated with anti-TNF agents are scant, the strong immunosuppressive effect of these drugs implies a potential risk of cancer.

## Acute uveitis, Crohn's disease, and sarcoidosis

Acute uveitis, Crohn's disease, and sarcoidosis are other adverse events that have been rarely associated with etanercept therapy in AS patients. Several anecdotal reports and a study using observations from two drug event databases have suggested that etanercept may be responsible for flare-ups or new occurrences of acute anterior uveitis.[86] In contrast, other data have shown that etanercept may prevent acute uveitis in AS, although less effectively than infliximab.[87]

In this regard, a systematic review of the literature was recently conducted in order to analyze the effectiveness of immunosuppressants and biologic therapies in patients with autoimmune posterior uveitis, chronic anterior uveitis associated with juvenile idiopathic arthritis, and macular edema. The authors concluded that biologic therapies (except for etanercept and daclizumab in Behcet's disease) are beneficial for the treatment of autoimmune uveitis. They did not consider etanercept to be as effective in autoimmune uveitis, as per recommendation A, evidence level 1b.[88] Therefore, considering all the available data, it seems likely that etanercept is not as effective as the anti-TNF-α monoclonal antibodies in treating and preventing acute uveitis.[89]

Unlike the other two TNF-α inhibitors, etanercept is not effective in controlling active Crohn's disease.[40] In fact, new-onset Crohn's disease has been described in AS patients with

etanercept.[90] Crohn's disease may be considered an immune-mediated injury induced by etanercept, but the causative role of etanercept has not been demonstrated at this point.

Paradoxical development of sarcoidosis in patients on etanercept therapy has been reported in patients with spondyloarthritis.[87,91,92]

### Geriatric patients

An interesting issue regarding the safety profile of etanercept therapy is its use in geriatric patients, who may be more prone to develop adverse events. However, elderly patients are usually excluded from randomized clinical trials. A retrospective analysis of trials with etanercept in rheumatoid arthritis, AS, and psoriatic arthritis, has shown that for patients ≥65 years, the rate of adverse events and serious adverse events was not higher than for younger patients.[93]

### Pregnancy

Neither animal studies nor prospective, controlled human studies have shown an increased rate of adverse outcomes after exposure to etanercept during pregnancy.[94] Nevertheless, their use during pregnancy is still controversial, because it remains unclear whether the benefits of treatment might be outweighed by potential teratogenicity or adverse effects on the course of pregnancy. Based on the available literature, experts suggest that continuation of treatment with TNF-α blockers is justified in pregnant patients with high disease activity and disease progression.[95–97]

### Fertility and breast-feeding

There are scarce data in the literature in regard to fertility in AS patients treated with etanercept, but we can find indirect evidence from some studies. The effect of TNF-α and TNF-α antagonists on semen quality in men is controversial. One study reported that infliximab infusion did not affect semen volume, sperm concentration, or forward progression, but that it did decrease sperm motility and the percentage of normal oval forms.[98] However, in another study done with sperm suspensions incubated with different doses of TNF-α, TNF-α plus infliximab, and infliximab alone, sperm motility and membrane integrity were higher in the samples incubated with TNF-α plus infliximab than in the samples treated with TNF-α or infliximab alone. This study demonstrates that exposing spermatozoa to increased concentrations of TNF-α results in a loss of functional and genomic spermatozoa integrity and that infliximab is capable of reversing the toxic effects induced by TNF-α.[99] Since the effects of possible transfer of etanercept to maternal milk in a still immature immune system are not known, in accordance with the risk/benefit principle, the use of etanercept is not recommended in breast-feeding women.[100]

## Conclusion

In the 12 years since commercialization of etanercept, its efficacy has been confirmed in AS, as shown in randomized clinical trials, open-label extension studies, and national registries. Etanercept is effective in different manifestations of the disease, including back pain, peripheral arthritis, enthesitis, and psoriasis. However, etanercept has shown no efficacy in inflammatory bowel disease, and its efficacy in the treatment of uveitis appears to be lower than that of the other anti-TNF drugs. Other aspects of AS, like radiographic progression, remain to be clarified in the future, since all the available anti-TNF agents have not shown efficacy in this regard to date. In the current economic crisis, etanercept has proved to be a useful drug, is able to maintain high rates of clinical remission when extending dosing intervals, and is efficacious when readministered after discontinuation of treatment. Regarding safety, up to 5 years of data from randomized clinical trials, open-label extensions, registries, and meta-analysis show that continuous long-term treatment with etanercept has a favorable risk-benefit ratio and no cumulative toxicity.

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## Disclosure

The authors report no conflicts of interest in this work.

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