# Etanercept in axial spondyloarthritis

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*To the Editor:* Axial spondyloarthritis (axSpA) is a chronic and progressive disease affecting the spine and sacroiliac (SI) joints, causing inflammatory back pain, stiffness, and inducing new bone formation (syndesmophytes and ultimately ankylosis in the severe forms). AxSpA consists of two subsets of patients: those with non-radiographic axSpA (nr-axSpA) and those with ankylosing spondylitis (AS), also known as radiographic axSpA. AxSpA is associated with substantial clinical and economic burdens for patients and the healthcare system. Patients with axSpA have physical limitations that can adversely affect employment, work productivity, leisure activities, mood, and interpersonal relationships.

Etanercept, one of the tumor necrosis factor inhibitors (TNFis), is effective in the treatment of spondyloarthritis, including AS, psoriatic arthritis (PsA), and juvenile idiopathic arthritis (JIA). A review published in 2017 has summarized the published data concerning the efficacy and tolerance of etanercept in axSpA.[1] This review will focus on summarizing the current published data concerning its drug reduction and impact on imaging progression and provide a brief discussion of an overview of etanercept in the management of axSpA.

In our study, we performed a systematic review on PubMed, covering the publish period between January 1, 2000, and April 1, 2021, using "etanercept" and "spondyloarthritis," "axial spondyloarthritis," or "ankylosing spondylitis" as keywords.

Etanercept is a dimeric fusion protein consisting of the extracellular domain of human TNF receptor (TNFR2 or p75), linked to the crystallizable fragment (Fc) of human type 1 immunoglobulin G (IgG1). The Fc component of etanercept contains the CH2 and CH3 domains and the hinge region, but not the CH1 domain of IgG [Figure 1A]. Etanercept is absorbed slowly from the site of subcutaneous injection, with time to peak concentration at approximately 48 to 60 hours, and is cleared slowly from the body with at 1/2 of 70 to 100 hours.[2]

With its approval by the European Medicines Agency in 2000, etanercept was one of the first TNFis approved for the treatment of autoimmune diseases other than rheumatoid arthritis (RA), including plaque psoriasis (including pediatric plaque psoriasis from the age of6 years), PsA, AS, and nr-axSpA, as well as polyarticular course JIA. However, etanercept has not been approved for the treatment of nr-axSpA in the US and the indications only cover the RA and AS in China. The recommended dose is 25 mg etanercept administered twice weekly, or 50 mg administered once weekly for the treatment of RA, PsA, AS, and nr-axSpA in adults. In children over 2 years old, the recommended dose is 0.4 mg/kg (up to a maximum dose of 25 mg) twice a week or 0.8 mg/kg (maximum 50 mg) once weekly. The American College of Rheumatology (ACR) recommendations considered its continuation with regular dose during first and second trimesters during pregnancy women and discontinuation in the third trimester if the disease is well controlled. Furthermore, the ACR considered etanercept compatible with breastfeeding with a strong recommendation.[3] Renal or hepatic impairments do not require any dose adjustment.

Etanercept with the extracellular domain of human TNFR2 (p75) can mimic the function of soluble TNF receptors, compete with transmembrane TNF receptors for binding to TNF, interfere with the binding of TNF to corresponding cells, thereby inhibiting its function [Figure 1B]. Etanercept binds TNFα in a 1:1 stoichiometry, while up to three molecules of mAb (adalimumab or infliximab) can bind to each soluble TNFα trimer. Regarding avidity, etanercept was shown to bind to soluble TNFα with a 10-fold to 20-fold greater avidity when compared with adalimumab or infliximab. In patients receiving treatment with etanercept, non-neutralizing antidrug antibodies (ADAs) were found which is binding to a portion of the drug molecule that is not essential to its therapeutic activity and does not interfere directly with the drug's therapeutic activity. Because

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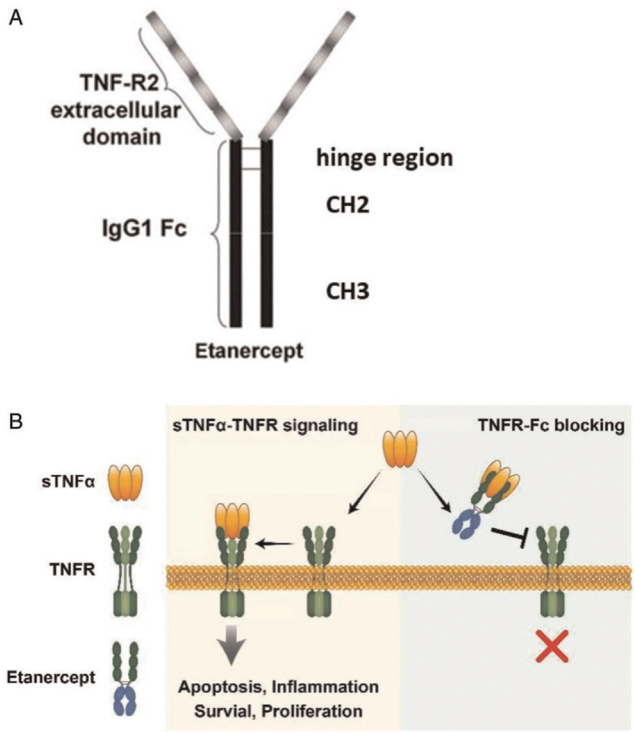


**Figure 1:** (A) Structures of etanercept. (B) Mechanism of etanercept. Fc: Crystallizable fragment; IgG: Immunoglobulin G; TNFR: TNF receptor.

etanercept does not carry the CHI domain of IgG1 which is important for the activation of C3, it induced complement-dependent cytotoxicity (induces apoptosis) much less potently than infliximab and adalimumab.[4]

Data from both short-term randomized controlled trials (RCTs) and long-term researches showed that etanercept was of good efficacy in the treatment of axSpA. A current open-label randomized controlled crossover clinical trial had a head-to-head comparison of etanercept and adalimumab in the treatment of AS. The results showed that they can both dramatically improve disease activity in 16 weeks and crossover administration of etanercept and adalimumab revealed comparable efficacy and safety.[5] The 10-year results of the ESTHER trial revealed that mean Bath Ankylosing Spondylitis Disease Activity Index and Bath Ankylosing Spondylitis Functional Index values of completers were more constantly <2 and mean Ankylosing Spondylitis Disease Activity Score <2.1 than those of non-completers.[6]

How about the timing of drug use? Current data from etanercept and other TNFis point toward bone marrow oedema magnetic resonance imaging (MRI) lesions as a valid target for early intervention, before the process of fat transformation, has started.[7] A current study shows that in patients with suspected non-radiographic axSpA with high disease activity but without the requirement of a positive finding on SI joint MRI and/or elevated C-reactive protein level, treatment with etanercept is not effective.[8] At present, many researches have shown that reducing the dose of etanercept after the patient has reached remission was also effective. A study in Italy in which the patients meeting the criteria for remission were randomized to receive subcutaneous etanercept as either 50 mg weekly (group 1) or 50 mg every other week (group 2). At the end of follow-up (the mean follow-up duration in group 1 and group 2 was 22.0 ± 1.0 months and 21.0 ± 1.6 months, respectively), 19 of 22 (86.3%) subjects in group 1 and 19 of 21 (90.4%) in group 2 were still in remission, with no significant difference between the two groups.[9] A retrospective study from China showed that remission >12 months before discontinuation/tapering helped to reduce relapse and tapering 25% of the etanercept dose every 3 months may be a pragmatic approach for more cost-effective use of the drug.[10]

The results of 6 years of ESTHER trial showed that the mean ± standard deviation change in the sacroiliitis sum score on radiographs was 0.13 ± 0.73, 0.27 ± 0.76, and 0.09 ± 0.68, in the time intervals baseline to year 2, year 2 to year 4, and year 4 to year 6, respectively, and findings indicate that long-term etanercept therapy decelerates the progression of structural damage in the SI joints.[11] A12-week randomized placebo-controlled trial in patients with nr-axSpA (EMBARK trial) showed that change in mean Spondyloarthritis Research Consortium of Canada (SPARCC) Sacroiliac Joint Structural Score was significantly greater for etanercept than placebo for erosion (–0.57 *vs.* –0.08, respectively) and backfill (0.36 *vs.* 0.06) which indicated that treatment with etanercept was associated with a significantly greater reduction in erosions and increase in backfill at 12 weeks compared with placebo.[12] From baseline to week 104 in the above trial, continued improvements in SPARCC MRI scores (SI joint: 26.0 and 23.4; spinal: 22.1 and 20.8) were seen in patients receiving etanercept/etanercept and placebo/etanercept.[13] The research of Dougados *et al*[14] showed that at 104 weeks, the total SI joint score improved in the etanercept group (*n* = 154, adjusted least-squares mean change: –0.14) and worsened in the control group (*n* = 182, change: 0.08) which suggests a lower rate of progression in the SI joint with etanercept than without anti-TNF therapy.

The radiological changes of the spine in axSpA are a topic of great concern. Previously, it was believed that TNFis did not slow the radiological progression of the spine. However, a growing number of researches have shown that the efficacy of TNFis is manifested when the duration of treatment is prolonged. A longitudinal analysis from the Alberta prospective cohort indicated that TNFis reduce spinal radiographic progression in patients with AS.[15]

The treatment of etanercept may increase the risk of serious infections (including active tuberculosis infection, invasive fungal infection, etc.), malignancies and lymphoproliferative disorders. There are few studies comparing the side effects of etanercept and monoclonal TNFis in the treatment of axSpA. Several studies from RA (or multiple autoimmune diseases) showed that the risk of severe infections, tuberculosis, and lymphoma with soluble-receptor TNFi therapy was lower than monoclonal TNFis.[16]

The use of TNFis dramatically improved the outcome of SpA; however, they engendered an immune response (immunogenicity). In a cross-sectional, observational study of patients with active RA or SpA experiencing

secondary failure to etanercept, infliximab, or adalimumab, ADAs were found in 114/570 (20.0%) of patients, and 51/188 (27.1%) against infliximab and 63/217 (29.0%) against adalimumab; none against etanercept.[17]

TNFis can effectively improve the condition of patients with axSpA. Etanercept, as a TNF receptor antibody fusion protein, can bind to soluble TNF with a high affinity to inhibit TNF activity. Data from both short-term RCTs and long-term researches showed that etanercept was of good efficacy in the treatment of axSpA. Moreover, the immunogenicity of etanercept is lower than other types of TNFi. Currently, the etanercept is already covered by Chinese medical insurance. Some cities, such as Beijing, have reimbursement rates as high as 80%. Today, etanercept is a promising option with good cost performance for the treatment of axSpA.

### *Conflicts of interest*

None.

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