

# Etanercept Versus Monoclonal Antibodies in Axial Spondyloarthritis: Game Over?



More than 10 years of experience with anti-tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) therapy in ankylosing spondylitis (AS) has brought us new therapeutic players. As respectively infliximab (IFX), etanercept (ETN), adalimumab, golimumab, and certolizumab were introduced, we were confronted with new modes of administration. However, regarding efficacy on axial and peripheral manifestations, all 5 actors seem somewhat equipotent. Also, IFX, ETN, adalimumab, and golimumab have already shown longterm efficacy after 2 to 8 years in established AS<sup>1,2,3,4</sup>. Nevertheless, treatment with TNF- $\alpha$  blocking agents such as adalimumab and ETN has shown similar high efficacy, with up to 54.5% ASAS40 (Assessment of Spondyloarthritis international Society 40%) response in early disease<sup>5,6</sup>. In this issue of *The Journal*, Song, *et al* report results on the longterm efficacy of ETN in patients with early axial spondyloarthritis (axSpA)<sup>7</sup>.

**Efficacy of TNF- $\alpha$  blocking agents.** Generally speaking, 2 types of TNF- $\alpha$  therapy are distinguished: ETN, a soluble TNF- $\alpha$  receptor antagonist, and monoclonal antibodies. All TNF blocking agents display similar short-term efficacy in axSpA<sup>4,8,9,10,11,12</sup> (Figure 1). Adalimumab displayed sustained clinical efficacy after 2 years of treatment with an ASAS40 response of 39.4% at Week 24 to an ASAS40 response in 50.6% after 2 years<sup>2,10</sup>. Also IFX maintained ASAS20 response of 84.8% after 8 years of treatment<sup>13</sup>. Similar results can be found in ETN and golimumab after 2 years<sup>3,4</sup>. However, all of these followup studies have been published in AS, generally comprising patients with longer disease duration and more progressive disease.

Song, *et al* provide the longterm data of the ESTHER trial with ETN over 3 years. Initially, AS and nonradiographic axSpA (nr-axSpA) with a disease duration of less than 5 years and active inflammation on magnetic resonance imaging (MRI) were treated with ETN or sulfasalazine (SSZ) during a 48-week period. ETN-treated patients responded better regarding MRI inflammation and clinical

response than did the SSZ group<sup>14</sup>. Afterward, all patients were switched to ETN and displayed similar response rates in AS and nr-axSpA, provided that baseline characteristics were comparable<sup>6</sup>. Notably, the mean disease duration was 2.7 years, depicting early disease. Clinical response was consistently maintained over 1, 2, and even 3 years in both groups with ASAS partial remission obtained in 43.9% of patients. In fact, no differences regarding response of objective markers such as MRI scores and C-reactive protein, or clinical disease activity markers such as Bath AS Disease Activity Index or AS Disease Activity Score, could be detected over time between AS and nr-axSpA. However, we must underline the high dropout rate of almost 50% during this followup period. Therefore these results should be interpreted with caution.

**Extraarticular manifestations.** Many clinical trials and observational cohorts have shown some inferiority when it comes to the treatment of the extraarticular manifestations (EAM) in SpA. Regarding the treatment of acute anterior uveitis, monoclonal antibodies have proven effective. The effect of ETN, however, is less pronounced. The initial clinical trials in inflammatory bowel disease have shown no efficacy in treatment with ETN<sup>15,16</sup>.

On the other hand, in SpA-related skin disorders such as psoriasis, the receptor antagonist displays a dose-response relationship, with high dosage of the drug to suppress skin inflammation in a comparable degree to monoclonal antibodies. Psoriasis Area and Severity Index 75 could be achieved in only 26%, possibly underlining the insufficient disease control with ETN in psoriatic arthritis<sup>17</sup>.

Unfortunately, no longterm ESTHER data regarding EAM are reported in this article. Therefore the longterm effect of ETN on these EAM in early disease remains to be determined.

**Safety.** Considering various registries across the globe, the overall risk of serious infections associated with anti-TNF is reassuring, especially in young patients and in compari-

*See Good response with etanercept in axial SpA, page 2034*

## ASAS40 response (week24)

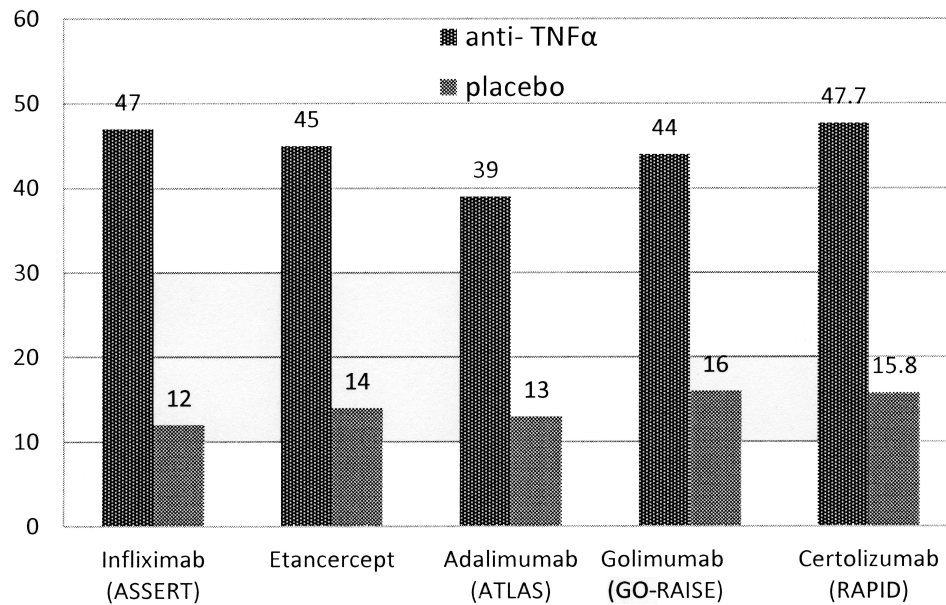


Figure 1. Clinical efficacy of anti-tumor necrosis factor (TNF)- $\alpha$  agents in ankylosing spondylitis<sup>4,8,9,10,11,12</sup>. ASAS: Assessment of Spondyloarthritis international Society (guidelines).

son to other nonbiologic disease-modifying antirheumatic drugs (DMARD). The British registry (BSRBR) presented adjusted hazard ratios declining from 1.8 in the first 6 months to 1.3 in the following months without clear differences across the 3 actors<sup>18</sup>. The DREAM registry, however, introduced a more generous profile in favor of ETN to IFX and adalimumab, which presented a 2-fold higher risk of serious infections<sup>19</sup>. Similar findings were reported in the US Safety Assessment of Biologic Therapy registry<sup>20</sup>. Also, the risk of tuberculosis (TB) and opportunistic infections is remarkably higher in monoclonal antibodies in comparison to ETN<sup>21</sup>.

Overall, anti-TNF did not show an increased risk of solid malignancies or lymphoma, except for some contradictory reports of a slightly higher risk for non-melanoma skin cancer<sup>22</sup>. The higher incidence of lymphoma is a known phenomenon in inflammatory diseases, especially rheumatoid arthritis. There are recent data from the BSRBR suggesting a beneficial effect of ETN on the occurrence of mortality and lymphoma in comparison to other DMARD and monoclonal antibodies, but this needs to be confirmed<sup>23</sup>.

Occurrence of adverse events in 3 year followup of ETN in axSpa consisted mainly of mild upper respiratory tract infections. Only one case of a serious adverse event of sarcoidosis could possibly be linked to ETN therapy. No opportunistic infections, TB, or malignancies were observed. There is ample evidence from registries about the safety profiles of the biologicals regarding infections,

malignancies, and overall safety over time, compared to the general population and other DMARD. This setting is more appropriate for the safety evaluation than the “long”-term followup of a small sample size in a clinical trial setting.

**Structural damage.** The evaluation of radiographic progression is usually performed by the modified Stokes AS spinal score (mSASS). It has been extensively evaluated and validated, despite its known limitations (inclusion of both erosive and osteoproliferative features, and the neglect of the thoracic spine). Initially, anti-TNF failed to deliver the anticipated effect on radiographic progression by reduction of MRI inflammation. However, this was mainly due to the quality of the comparative cohort, the low sensitivity of mSASS, and the inadequate followup period. Haroon, *et al* could demonstrate a 50% reduction in progression as a result of anti-TNF therapy comparing radiographs more than 1.5 years apart<sup>24</sup>. Also, several authors have provided data in which patients treated with anti-TNF were followed prospectively for 8 years<sup>25,26</sup>. Considering Baraliakos, *et al*<sup>25</sup>, a difference in progression rate was seen only in the second half of the observation. Strikingly, both groups in both studies exhibited radiographic progression despite “optimal” therapy. The latter findings and the discovery that up to 64% of patients in Ankylosing Spondylitis Disease Activity Score inactive disease and 72% of patients in ASAS partial remission show active inflammation on MRI of the sacroiliac joints or spine under ETN treatment in the ESTHER trial by Song, *et al*, support the presence of silent disease activity in the absence of overt clinical signs. The

effect of this residual disease activity on the longterm structural progression therefore remains to be determined.

TNF- $\alpha$  blocking agents, and most recently ETN, have displayed similar efficacy in short and longterm followup studies in early disease. They do, however, show some discrepancies in the management of extraarticular manifestations and safety profiles.

Regarding the choice of anti-TNF- $\alpha$ , an individual assessment of the patient should be made. Age, comorbidities, concomitant medication, and overall immunosuppression, extraarticular manifestations, risk of infection, living conditions, and even regional aspects (for example, exposure risk to TB) need to be taken into account regarding the choice of anti-TNF- $\alpha$  for the individual patient. The favorable safety profile of ETN may be crucial in some vulnerable patients, whereas the suppression of a recurrent uveitis may be the main clinical problem in others.

As demonstrated by Song, *et al*, clinical remission may not reflect MRI remission, which highlights the importance of MRI, also in followup. However, additional data regarding the differential evolution of MRI-positive and MRI-negative patients are needed.

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