



Comment on the clinical efficacy and safety of etanercept versus sulfasalazine in patients with ankylosing spondylitis (the ASCEND trial)

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Abstract

The ASCEND trial claimed that etanercept was superior to sulfasalazine (SSZ) in the treatment of ankylosing spondylitis and proposed that earlier initiation of anti-TNF treatment was feasible. However, the high response rate with SSZ and the absence of a placebo group cast doubts on this conclusion. In addition, safety was not an appropriate issue since the study was not powered to evaluate it and the follow-up period was insufficient.

Key words: Ankylosing spondylitis, etanercept, sulfasalazine

Dear Editor,

Sulfasalazine (SSZ) has been the most widely used treatment for spondyloarthritis although its efficacy is not clear. Its use in patients with peripheral arthritis was advised in the ASAS and EULAR guidelines for the management of ankylosing spondylitis (AS).^[1] However, evidence for the efficacy for spinal symptoms is contradictory. Dougados et al showed in their randomized controlled study that SSZ was an effective treatment for AS patients without peripheral arthritis or gastrointestinal symptoms.^[2] In a following investigation Braun et al. found no major difference between SSZ and placebo groups in patients with undifferentiated spondyloarthritis or early AS.^[3] Subgroup analysis revealed that patients with peripheral arthritis did not benefit from SSZ and that the only determinant for response was inflammatory back pain. In the most recent systematic literature review for the ASAS/EULAR recommendations authors

reported that there is no effect of SSZ on any variable related to AS.^[4]

The situation became more confusing after a recent study from Braun et al.^[5] In this randomized, double-blind controlled study the authors showed that etanercept was more effective than SSZ in ameliorating both the axial and peripheral manifestations of AS, as early as the second week of treatment. However, there are some issues that need to be clarified:

1- This study was designed for testing the superiority of etanercept in comparison to SSZ. However, safety was not an appropriate end point since the study was not powered to show the differences between the side effects among the study groups. In fact a recent survey also showed that most of randomized clinical trials with anti-TNF agents in rheumatologic diseases were inappropriately labeled as both efficacy and safety studies despite their lack of power.^[6] Moreover, 16 weeks may not be suitable to evaluate safety. Additionally, patients with

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significant concurrent medical conditions or other relevant comorbidities were excluded.

2- Efficacy of SSZ may have been underestimated in this study due to several reasons. First, patients were randomly assigned to receive either etanercept 50 mg once weekly or SSZ. Patients in the SSZ group were put on an initial dose of 0.5 gr of SSZ and the dose was increased 0.5 gr each week until the target dose of 3 gr was reached. Therefore, full dosage was achieved by week 6 and the authors decided to choose 16-weeks of duration as the end-point based on the knowledge that optimal efficacy may take 4 months.^[7] However, it should be kept in mind that in a previous study, which the authors cited, the initial dosage of SSZ was 2 gr and the latent period of the onset of activity for SSZ was estimated as three months. Thus, 10 weeks might not be enough to reach maximum efficacy. Moreover, the absence of a placebo group may complicate the interpretation since a remarkably high proportion of patients (52.9% for SSZ in comparison with 75.9% for ETN group) achieved primary efficacy end-point of ASAS20. Additionally 32.6% in SSZ group (vs 59.8% in ETN group) achieved ASAS40 and 21.2% achieved ASAS5/6 (45.5% in ETN group) response. These efficacy figures may be higher than expected with placebo.^[8-10] The conclusion of “earlier initiation of anti-TNF therapy may warrant consideration, specifically in place of treatment with sulfasalazine, in patients with active axial and peripheral AS” might not be appropriate due to the discussed limitations.

3- In the ASCEND study 566 AS patients enrolled at 85 centers in 23 countries. The effect of the centers on outcomes and the potential variation was not accounted for.

In conclusion, although it was shown that anti-TNF agents was superior to SSZ in the treatment of AS, before recommending the early initiation of anti-TNF agents in place of SSZ we need more carefully designed studies with appropriate power.

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