Objectives. Etanercept 50 mg a week is approved in the treatment of AS. Increasing the etanercept dose to 100 mg/week improves efficacy in cutaneous psoriasis, a clinical manifestation related to the spondylarthritides family, while maintaining its safety profile. The purpose of this study was to evaluate the efficacy and safety of etanercept 100 vs 50 mg/week in patients with AS.

Methods. Adult patients with AS were randomized to receive etanercept 50 mg twice a week (biw), or etanercept 50 mg once a week (qw) for 12 weeks. The primary efficacy endpoint was Ankylosing Spondylitis Assessment Study (ASAS20) response at Week 12; secondary endpoints included ASAS40, ASAS50, ASAS70 and ASAS5/6 responses, partial remission and quality of life. Safety was assessed until 15 days after the last visit.

Results. A total of 108 patients were randomly selected and treated, 54 in each arm. At 12 weeks, ASAS20 response was achieved by 34 (71%) out of 48 patients of the etanercept 50 mg biw group and by 37 (76%) out of 49 patients of the etanercept 50 mg qw group (not statistically significant differences). Other efficacy variables improved significantly over time, but not between treatment groups. Fifty-six patients experienced at least one adverse event (generally, infections and infestations, gastrointestinal disorders and injection site reactions), most of them mild or moderate.

Conclusions. High-dose (100 mg/week) etanercept in the treatment of AS for 12 weeks is as safe as the standard dose (50 mg/week). However, it does not significantly increase its efficacy.


Key words: Etanercept, Ankylosing spondylitis, Safety, Efficacy.
High-dose etanercept in AS

Introduction

AS is a chronic inflammatory disease characterized by axial and peripheral arthritis and enthesitis [1], which affects between 0.15 and 1.4% of the adult population [2]. About 80% of patients experience their first symptoms before the age of 30 years, with a proportion men: women of 2:1. More than 90% of susceptibility to AS is explained by genetic factors, but environmental factors, such as bacterial infections, have also been identified [1, 3]. The first-choice treatment in AS is NSAIDs [4, 5]. However, ~20% of patients do not improve with NSAIDs [5]. Other classic therapies in the treatment of rheumatic diseases, such as DMARDs or CSs, do not achieve an adequate control of disease activity [4, 6, 7]. Antagonists of TNF-α have been proved as a safe and effective alternative for AS, mainly for patients who are refractory to NSAIDs [3, 4]. TNF-α antagonists have a rapid effect on disease symptoms, normalizing acute-phase reactant levels and reducing inflammation in SI and spinal joints [3, 4], and their effects are prolonged for a long time [4, 8–10].

Etanercept is a fusion protein formed by a recombinant form of the human TNF soluble receptor p75, linked to the fragment crystallizable (Fc) portion of the human G1 immunoglobulin [11]. The safety and efficacy of etanercept in the treatment of AS has been proved in a large number of studies [9, 10, 12–15], and its use in AS treatment is approved in a regimen of 50 mg a week, both in Europe and in the USA. Adverse events related to etanercept are generally mild or moderate [9, 10, 12–15]. Recently, several studies have been conducted increasing etanercept dose from 50 to 100 mg/week for the treatment of psoriasis and RA. However, the results of these studies showed that increasing etanercept dose did not improve its efficacy [16–20], while maintaining its safety profile. To date, no studies have been done to test the efficacy and safety of etanercept 100 mg/week in the treatment of AS. Thus, the purpose of the present double-blind, 12-week randomized pilot study, is to evaluate the effect of etanercept 100 vs 50 mg/week to treat AS as well as its safety and tolerability profile.

Patients and methods

Subjects

Eligible patients were recruited in 15 Spanish centres. The whole study was primarily approved by the local ethical review board of the Hospital de Navarra, and secondarily by the ethical review boards of all participating hospitals, according to the principles of the Declaration of Helsinki. All patients received detailed information on the study and provided their written informed consent before their inclusion. Candidates were adult outpatients (18–70 years) with AS diagnosis as defined by the modified New York criteria for AS [21], and with inflammatory activity maintained for ≥12 weeks, who had failed treatment with at least two NSAIDs at maximum recommended doses during at least 3 months. In patients with predominantly axial forms, inflammatory activity was defined by a BASDAI ≥4 and at least one of the following: patient’s global disease assessment ≥4; spinal pain ≥4 on a visual analogue scale (VAS); and/or increase in ESR and/or CRP above normal laboratory levels. In patients with predominantly peripheral forms, inflammatory activity was defined by arthritis or enthesis in at least one site, together with patient’s global disease assessment ≥4 and/or increase in ESR and/or CRP above normal laboratory levels. Women had a negative pregnancy test and, if sexually active, both men and women used medically acceptable contraceptive methods.

Patients with complete ankylosis of the spine were ineligible. Patients were also excluded if they had contraindications for the treatment with anti-TNF, or if they needed to start treatment with DMARDs or with prednisone (or equivalent) >10 mg/day. Other non-permitted treatments were more than one NSAID in the 2 weeks before baseline, IA CSs or any live vaccine in the 4 weeks before the screening visit, any investigational drug within 3 months of the screening visit, and TNF-α inhibitors or other biological drugs at any time. Abnormalities in haematological profiles, important comorbid medical conditions, psoriasis, psychiatric disease, or history of alcohol or drug abuse, were reasons for exclusion. Pregnant or breastfeeding women were also ineligible. Previous history of uveitis was not an exclusion criterion.

Randomization and treatment

Patients were sequentially numbered at the screening visit. Upon completion of the baseline evaluation, eligible subjects were randomly allocated to a treatment group. Patients remained in their treatment group until the end of the study. All study personnel and participants, including statisticians, were blinded to treatment assignment for the whole duration of the study.

Patients were randomly selected to receive either etanercept 50 mg twice a week (biw) or 50 mg once a week (qw) plus a second injection of placebo. At the baseline visit, patients were instructed about the reconstitution of the vials and self-administration of the treatment. Each dose was injected at a different site, including abdomen, thigh or upper arm, at the same hour of the day (±4 h) and on the same day of the week [every 72 (±24 h)]. No adjustments in the dose of etanercept were permitted; however, temporary suspension due to adverse events was permitted for up to 2 weeks. Changes in concomitant treatments were not allowed.

Study objectives

Our main aim was to evaluate the efficacy of etanercept 50 mg biw vs 50 mg qw in patients with AS who had previously failed the standard therapies. Time to treatment’s initial response, the effect on the response criteria, and the safety and tolerability profile of the two treatment regimens were secondary objectives of this study.

Efficacy endpoints

The primary efficacy endpoint was the proportion of subjects who achieved Ankylosing Spondylitis Assessment
Study (ASAS20) [22] response at Week 12. Patients’
global assessment of disease activity and pain were mea-
measured using a VAS, physical function was assessed using the
BASFI score [23] and inflammation was measured using the score of the morning-stiffness items of the
BASDAI [24]. Secondary endpoints were the proportion of
subjects who achieved ASAS40, ASASS0, ASAS70
[25], ASAS5/6 [26] response and partial remission at
Week 12, nocturnal and overall spine pain, physician
global assessment of disease activity, activity index (BASDAI), spinal mobility (BASMI) score [27], complete
peripheral joint count (ACR66/64 index), tenderness of
enthesis [Maastricht Ankylosing Spondylitis Enthesis
Score (MASES) index] [28], CRP and ESR. Finally, quality
of life was assessed by the European Quality of Life Scale
(EuroQoL) [29] and 36-item Short-Form Health Survey
(SF-36) questionnaires [30].

Safety endpoints
Safety was assessed by the evaluation of the percentage
and type of adverse events and serious adverse events,
vital signs, physical examination, early withdrawals and
laboratory results. Safety was assessed during all the
study, until ~15 days after the last study visit. All patients
who received at least one etanercept dose were included
in the safety analysis.

Sample size
In order to determine and assess response in terms of
ASAS20 at 12 weeks of treatment with etanercept 100
vs 50 mg/week, 108 patients were enrolled, 54 per arm.
This sample size was calculated to allow to detect differ-
ences of at least 25% between treatments ($P = 0.05$,
two-sided, 80% contrast power). A 10% replacement
rate was estimated.

Statistical methods
All randomized patients who had received at least one
treatment dose and who had undergone at least one ther-
apy evaluation were included in the intent-to-treat (ITT)
population. Of them, those who fulfilled study procedures
without major deviations and received at least 80% of in-
jections (at least 19) were considered as per-protocol (PP)
population. Efficacy and safety analysis were performed
on the ITT population. Furthermore, the primary efficacy
endpoint was also analysed in the PP population.

Qualitative variables were described using absolute
and relative frequencies; quantitative variables by means
of centralization and dispersion measures. To determine
changes from the baseline visit in each primary endpoint,
association tests were performed between visits using the
Wilcoxon test for continuous variables, the McNemar
test for discreet dichotomic variables or the Sign test for
non-dichotomic ordinal discreet variables. Responders’
rate was evaluated in terms of ASAS after 12 weeks of
treatment. Two-sided significance tests ($P = 0.05$) were
used.

Results
Data were collected between January 2007 and March
2008. Out of 126 screened patients, 108 were randomly
selected and treated, 54 in each arm of the study. Of
them, 97 were considered PP population (Fig. 1). The rea-
sons for the exclusion of 11 patients from PP analysis
were protocol deviations (7 patients), adverse events
(2 patients), patient decision (1 patient) and other reasons
(1 patient). The number of received injections and weeks
on treatment were equivalent between groups.

Patient’s demographics are shown in Table 1. Baseline
and Weeks 2 and 12 clinical data are summarized in
Table 2. Baseline differences between groups were only
found in HLA-B27, which was more frequently found
among patients assigned to etanercept 50 mg biw ($P = 0.04$). Baseline quality of life and changes at Week 12 are summarized in Table 3. The eight dimensions of
the SF-36 questionnaire were reduced to two dimensions:

- a physical component summary (PCS) score and a mental
component summary (MCS) score. EuroQoL results were
categorized in patients with problems and patients with-
out problems. No significant differences were found be-
tween groups in baseline quality of life.

Efficacy
In the ITT analysis, at Week 12, ASAS20 response was
achieved by 34 (71%) out of 48 patients of the etanercept
50 mg biw group and by 37 (76%) out of 49 patients of the
etanercept 50 mg qw group (Fig. 2A). The differences were
not statistically significant. Similarly, ASAS40, ASASS0,
ASAS70 and ASAS5/6 responses were not significantly
different between both groups (Fig. 2A). At 12 weeks, par-
tial remission was achieved by 14 (29%) out of 48 patients
of the etanercept 50 mg biw group and by 13 (27%) out of
49 patients of the etanercept 50 mg qw group. Per PP
population analysis of ASAS20 response gave similar re-
results, without significant differences. ASAS responses at
Week 2 are shown in Fig. 2B.

The values at Weeks 2 and 12 for nocturnal and overall
spinal pain, patient and physician global assessment,
BASFI, BASDAI, BASMI, swollen and painful joint count,
MASES index, CRP and ESR are summarized in Table 2.
BASDAI scores at all visits are shown in Fig. 3A. All par-
ameters were significantly reduced at Week 2 ($P < 0.05$ or
0.0001) in both treatment groups. Exceptions were found
in the etanercept 50 mg biw group for BASMI and the
count of painful joints, which were significantly reduced
at Week 4, and for the number of swollen joints counts,
which was significantly reduced at Week 8. The proportion
of patients reaching a 50% improvement in the BASDAI
score at Week 2 was 53% in patients treated with etaner-
cept 50 mg biw and 43% in patients treated with etaner-
cept 50 mg qw (Fig. 3B). These proportions increased to
67 and 63% for etanercept 50 mg biw and etanercept
50 mg qw, respectively, at Week 12. No significant differ-
ences were found in any efficacy endpoint between treat-
ment groups.

Changes in quality of life from baseline to Week 12 are
shown in Table 3. Both the SF-36 questionnaire and the
Fig. 1 Flow diagram of a multicentre, randomized trial comparing etanercept 50 mg biw or etanercept 50 mg qw plus a second placebo dose, in patients with AS.

![Flow diagram](Image)

**Table 1** Baseline demographic and clinical data

<table>
<thead>
<tr>
<th></th>
<th>Etanercept 50 mg biw (n = 54)</th>
<th>Etanercept 50 mg qw (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), median, years</td>
<td>40.22 (10.36), 41.06</td>
<td>42.63 (10.66), 41.97</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>43 (79.63)</td>
<td>43 (79.63)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (20.37)</td>
<td>11 (20.37)</td>
</tr>
<tr>
<td>History of AS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since diagnosis, mean (s.d.), median, years</td>
<td>7.03 (6.83), 4.76</td>
<td>7.28 (7.06), 4.93</td>
</tr>
<tr>
<td>Spine pain symptoms duration, mean (s.d.), median, years</td>
<td>11.87 (8.45), 10.00</td>
<td>14.35 (10.52), 12.00</td>
</tr>
<tr>
<td>Family history of AS, n (%)</td>
<td>45 (83.33)</td>
<td>45 (83.33)</td>
</tr>
<tr>
<td>HLA-B27, <em>n</em> (%)</td>
<td>48 (90.57)</td>
<td>40 (74.07)</td>
</tr>
<tr>
<td>Concomitant medication, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>45 (83.33)</td>
<td>48 (88.89)</td>
</tr>
<tr>
<td>DMARDs</td>
<td>16 (29.63)</td>
<td>15 (27.78)</td>
</tr>
<tr>
<td>CSs</td>
<td>6 (11.11)</td>
<td>5 (9.26)</td>
</tr>
</tbody>
</table>

*a*Missing data from six or less patients. *P < 0.05.*
**Table 2** Pain and disease activity at baseline, Weeks 2 and 12

<table>
<thead>
<tr>
<th>Pain and disease activity</th>
<th>Baseline (n = 54)</th>
<th>Week 2 (n = 51)</th>
<th>Week 12 (n = 48)</th>
<th>Etanercept 50 mg biw</th>
<th>Etanercept 50 mg qw</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nocturnal back pain, mean (S.D.), median</td>
<td>6.76 (2.15), 7.05</td>
<td>6.40 (2.55), 6.95</td>
<td>6.36 (2.87), 3.20**</td>
<td>3.58 (2.58), 3.60**</td>
<td>3.95 (2.44), 3.70**</td>
</tr>
<tr>
<td>Total back pain, mean (S.D.), median</td>
<td>6.74 (2.31), 7.50</td>
<td>6.30 (2.31), 6.25</td>
<td>3.87 (2.84), 3.20**</td>
<td>5.00 (4.54), 4.20**</td>
<td>3.95 (2.44), 3.70**</td>
</tr>
<tr>
<td>Disease activity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Physical global assessment, mean (S.D.), median</td>
<td>6.01 (1.26), 6.00</td>
<td>5.82 (1.03), 5.90</td>
<td>3.22 (1.84), 3.20**</td>
<td>3.01 (1.49), 3.20**</td>
<td>4.02 (2.55), 3.60**</td>
</tr>
<tr>
<td>Etanercept 50 mg qw</td>
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<td></td>
<td></td>
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<tr>
<td>Pain</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nocturnal back pain, mean (S.D.), median</td>
<td>6.75 (2.05), 6.00</td>
<td>6.97 (2.02), 6.90</td>
<td>4.02 (2.55), 3.60**</td>
<td>3.84 (2.44), 4.20**</td>
<td>3.84 (2.44), 4.20**</td>
</tr>
<tr>
<td>Total back pain, mean (S.D.), median</td>
<td>6.87 (2.09), 6.29</td>
<td>6.48 (1.81), 6.22</td>
<td>4.13 (2.80), 3.99**</td>
<td>4.06 (2.35), 4.01**</td>
<td>4.06 (2.35), 4.01**</td>
</tr>
<tr>
<td>Disease activity</td>
<td></td>
<td></td>
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<tr>
<td>Physical global assessment, mean (S.D.), median</td>
<td>6.40 (2.10), 3.00</td>
<td>3.10 (2.24), 3.00</td>
<td>3.58 (2.53), 3.30**</td>
<td>3.69 (2.33), 3.62**</td>
<td>3.69 (2.33), 3.62**</td>
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<tr>
<td>Etanercept 50 mg qw</td>
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<tr>
<td>Pain</td>
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<td></td>
</tr>
<tr>
<td>Nocturnal back pain, mean (S.D.), median</td>
<td>0.50 (1.59), 0.00</td>
<td>0.61 (2.52), 0.00</td>
<td>0.22 (0.86), 0.00</td>
<td>0.02 (0.14), 0.00**</td>
<td>0.02 (0.14), 0.00**</td>
</tr>
<tr>
<td>Total back pain, mean (S.D.), median</td>
<td>3.28 (6.42), 0.00</td>
<td>4.04 (11.30), 0.00</td>
<td>3.22 (10.97), 0.00</td>
<td>2.13 (6.61), 0.00**</td>
<td>2.13 (6.61), 0.00**</td>
</tr>
<tr>
<td>Disease activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical global assessment, mean (S.D.), median</td>
<td>2.55 (3.39), 1.00</td>
<td>2.46 (3.33), 1.00</td>
<td>1.88 (3.32), 0.00**</td>
<td>0.83 (1.54), 0.00***</td>
<td>0.83 (1.54), 0.00***</td>
</tr>
<tr>
<td>Etanercept 50 mg qw</td>
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<tr>
<td>Pain</td>
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</tr>
<tr>
<td>Nocturnal back pain, mean (S.D.), median</td>
<td>17.05 (20.54), 9.29</td>
<td>20.95 (31.85), 9.40</td>
<td>17.05 (20.54), 9.29</td>
<td>20.95 (31.85), 9.40</td>
<td>20.95 (31.85), 9.40</td>
</tr>
<tr>
<td>Total back pain, mean (S.D.), median</td>
<td>18.37 (16.77), 13.00</td>
<td>22.62 (16.04), 18.50</td>
<td>18.37 (16.77), 13.00</td>
<td>22.62 (16.04), 18.50</td>
<td>22.62 (16.04), 18.50</td>
</tr>
</tbody>
</table>

*Missing data from four or less patients. *P < 0.05 vs baseline. **P < 0.001 vs baseline. ***P < 0.05 between groups.

**Discussion**

The results of this study show that the use of etanercept in patients with AS, both in two weekly 50 mg doses and in one weekly 50 mg dose, improves disease activity, physical function and quality of life. However, the administration of etanercept in a dose of 50 mg per week did not produce a significant improvement in AS symptoms as compared to placebo.

**Safety**

The safety population included all patients who received at least one etanercept dose. Fifty-six patients experienced adverse events at least once in the etanercept group, 29 in the placebo group, and 21 in the placebo group with topical CSs. The most common adverse events were infections and infestations (11 out of 54 in etanercept 50 mg biw and 14 out of 54 in etanercept 50 mg qw).

**Table 4** The most common adverse events were infections and infestations (11 out of 54 in etanercept 50 mg biw and 14 out of 54 in etanercept 50 mg qw).

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo 50 mg biw (n = 54)</th>
<th>Placebo 50 mg qw (n = 54)</th>
<th>Placebo 50 mg biw (n = 54)</th>
<th>Placebo 50 mg qw (n = 54)</th>
<th>Placebo 50 mg biw (n = 54)</th>
<th>Placebo 50 mg qw (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>9 (17%)</td>
<td>9 (17%)</td>
<td>9 (17%)</td>
<td>9 (17%)</td>
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<tr>
<td>Adverse event</td>
<td>9 (17%)</td>
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<tr>
<td>Adverse event</td>
<td>9 (17%)</td>
<td>9 (17%)</td>
<td>9 (17%)</td>
<td>9 (17%)</td>
<td>9 (17%)</td>
<td>9 (17%)</td>
</tr>
</tbody>
</table>

**Conclusion**

The use of etanercept in patients with AS, both in two weekly 50 mg doses and in one weekly 50 mg dose, improves disease activity, physical function and quality of life. However, the administration of etanercept in a dose of 50 mg per week did not produce a significant improvement in AS symptoms as compared to placebo.
TABLE 3 Quality of life

<table>
<thead>
<tr>
<th>Quality of Life</th>
<th>Baseline</th>
<th>Change at Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Etanercept 50 mg biw (n = 54)</td>
<td>Etanercept 50 mg qw (n = 54)</td>
</tr>
<tr>
<td>SF-36, mean (s.d.), median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS score</td>
<td>33.37 (14.61), 32.81</td>
<td>30.23 (13.79), 26.25*</td>
</tr>
<tr>
<td>MCS score</td>
<td>49.22 (16.86), 55.75</td>
<td>45.02 (17.87), 46.06</td>
</tr>
<tr>
<td>EuroQoL, patients with problems, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility</td>
<td>37 (68.52)</td>
<td>37 (68.52)</td>
</tr>
<tr>
<td>Self-care</td>
<td>36 (66.67)</td>
<td>37 (68.52)</td>
</tr>
<tr>
<td>Usual activities</td>
<td>48 (88.89)</td>
<td>44 (81.48)</td>
</tr>
<tr>
<td>Pain-discomfort</td>
<td>53 (98.15)</td>
<td>51 (94.44)</td>
</tr>
<tr>
<td>Anxiety-depression</td>
<td>25 (46.30)</td>
<td>30 (55.56)</td>
</tr>
</tbody>
</table>

*Missing data from two or less patients. *P < 0.01 vs baseline. **P < 0.001 vs baseline. ***P < 0.05 between groups.

Fig. 2 Percentage of patients achieving ASAS20, ASAS40, ASAS50, ASAS70 and ASAS5/6 responses (A) at Week 12 and (B) at Week 2.
with the standard dose. Although there are several studies supporting the lack of efficacy of the increasing doses of the TNF-\(\alpha\) antagonists in different chronic rheumatic diseases [16–20], this is the first one to focus on the evaluation of the efficacy of increasing doses of a TNF-\(\alpha\) antagonist (etanercept) for axial symptoms.

In past years, it has been proved that the administration of etanercept 50 mg in two weekly 25 mg doses produces a dramatic and sustained improvement in AS symptoms. Davis et al. [13] and Calin et al. [14] tested the efficacy of etanercept 50 mg/week vs placebo at 12 weeks. In both studies, the proportion of patients achieving ASAS20 response was higher among those receiving etanercept than in those treated with placebo, with significant results as early as Week 2. Other studies [9, 10] showed that the percentage of ASAS20 responders increased >80% up to 192 weeks. In our study, >70% of patients achieved ASAS20 response after 12 weeks of etanercept treatment. Although no direct comparison is possible, those results are better than those reported in other studies on AS with infliximab [31] and adalimumab [32] and similar to those reported for golimumab [33]. In accordance with previous studies [13, 14], in our study, ASAS50 response was achieved between 28 and 37% of patients (depending on the etanercept dose) at Week 2 and by >45% of patients at Week 12. ASAS40 response was achieved between 34 and 45% of patients at Week 2 and by >50% of patients at Week 12, whereas partial remission was achieved by ~17% of patients at Week 2 and by ~28% of patients at Week 12. Those results are slightly better than those reported for adalimumab [32, 34] and infliximab [31]. Other efficacy measures also improved in both groups of treatment, including nocturnal and global back pain, patient and physician global assessment, BASFI, BASDAI, BASMI,
Adverse events

<table>
<thead>
<tr>
<th>Severity of adverse events, n (%)</th>
<th>Etanercept 50 mg biw (n = 54)</th>
<th>Etanercept 50 mg qw (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>43 (84.31)</td>
<td>44 (88.00)</td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (9.60)</td>
<td>4 (8.00)</td>
</tr>
<tr>
<td>Severe</td>
<td>3 (5.88)</td>
<td>2 (4.00)</td>
</tr>
<tr>
<td>Adverse events (~3%), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>7 (13.00)</td>
<td>8 (14.80)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis/upper respiratory tract infection</td>
<td>5 (9.60)</td>
<td>8 (14.80)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>0 (0.00)</td>
<td>2 (3.70)</td>
</tr>
<tr>
<td>Abnormal laboratory tests, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transaminases increased</td>
<td>4 (7.40)</td>
<td>4 (7.40)</td>
</tr>
<tr>
<td>Other disorders, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (3.70)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1 (1.85)</td>
<td>2 (3.70)</td>
</tr>
<tr>
<td>Procedural dizziness</td>
<td>3 (5.55)</td>
<td>2 (3.70)</td>
</tr>
</tbody>
</table>

High-dose etanercept in 12-week AS treatment was as safe as the standard dose in the treatment of AS. Quality of life consistently improved in all domains for both etanercept doses; significant differences between doses were only found in the pain–discomfort domain. However, these results are difficult to interpret. In conclusion, the administration of high-dose etanercept (100 mg/week) in the treatment of AS for 12 weeks did not lead to significant improvement in AS symptoms as compared with the standard dose.

Rheumatology key messages

- High-dose etanercept in 12-week AS treatment did not significantly improve symptoms, as against the standard dose.
- High-dose etanercept in 12-week AS treatment was as safe as the standard dose.

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Consistently with the results obtained in psoriasis [16–18] and RA [19, 20] high-dose etanercept studies, in our work no differences were found between groups in the number and severity of adverse events; most of them being mild or moderate. In the PRESTA study [18], 4% of the patients receiving high-dose etanercept and 3% of patients receiving 50 mg/week had serious treatment-emergent adverse events. However, in our study only 1 out of 54 patients treated with 50 mg biw and 2 out of 54 patients treated with 50 mg qw had serious adverse events. The most frequent adverse events found in previous high-dose etanercept studies [16–18] were injection-site reactions, headache and upper respiratory infections. Equally, in our study the most frequent adverse events found were injection-site reactions and upper respiratory infections, without significant differences between groups. The occurrence of uveitis in our study was much lower than that observed in the previous studies [9, 10, 13]. Only one patient, with previous history of uveitis, on etanercept 100 mg/week, reported this manifestation. Therefore, considering all the adverse events found in the present study, high-dose etanercept was shown to be as safe as the standard dose in the treatment of AS.
References

High-dose etanercept in AS


