Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly

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Objectives. The objective of this study was to assess the humanistic impact of ankylosing spondylitis (AS), and compare the effect of etanercept 50 mg once-weekly (QW), etanercept 25 mg twice-weekly (BIW) and placebo on patient-reported outcomes (PROs).

Methods. In a 12-week, double-blind, placebo-controlled multicenter study, 356 patients with active AS received etanercept 50 mg QW, etanercept 25 mg BIW or placebo (3:3:1 randomization, respectively). PROs were assessed using Bath Ankylosing Spondylitis Functional Index, Bath Ankylosing Spondylitis Activity Index fatigue item, EuroQOL-5D (EQ-5D) utility, EQ-5D visual analog scale and the Medical Outcomes Short Form Questionnaire (SF-36) scores at baseline and at regular intervals. Mean changes from baseline in PROs were analysed using analysis of covariance to assess differences between etanercept and placebo, or between the two etanercept groups.

Results. Consistent with earlier reports, AS was associated with quality of life (QOL) impairment and functional limitations, similar to or worse than cancer, congestive heart failure, diabetes or depression. Treatment with etanercept 50 mg QW or 25 mg BIW significantly improved QOL and functional status compared with placebo. High proportions of patients achieved clinically meaningful improvements in all PRO measures, including physical function, fatigue, pain, psychosocial domains and general health status. Improvements were similar with the two etanercept dose regimens.

Conclusions. The more convenient etanercept 50 mg QW dose regimen significantly improves function and QOL in patients with AS, similarly to the standard dosing of 25 mg BIW, supporting its use for AS therapy.

KEY words: Etanercept, Ankylosing spondylitis, Patient-reported outcomes, Quality of life.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease characterized by insidious inflammation of the spine and sacroiliac joints leading to pain persisting for more than 3 months [1]. Other features of AS may include inflammation of the peripheral joints, entheses, eye and intestines. AS prevalence varies among ethnic groups and geographic locations [1], ranging from 0.55% to 1.4% [2–4]. The disease is generally diagnosed in the second or third decade of life, with higher prevalence and severity among men compared with women [1]. There is no predictable pattern of disease progression; however, AS can lead to significant functional impairment, work disability and reduced quality of life (QOL) [1, 5]. Pain, stiffness, fatigue and sleep problems are often reported by patients with AS as major difficulties affecting their ability to function [6]. Although reduced physical functioning is well recognized in those with AS [6–8], the impact on social and mental health aspects has not received as much attention. The limited literature available suggests that the disease impact on psychosocial dimensions is less marked than the physical aspects; nevertheless, psychosocial domains of health-related QOL are considerably diminished compared with that in the general population [6–8]. Early therapeutic interventions that would alter disease progression and delay functional disability may result in reducing the burden of the disease.

Until recently, limited treatment options were available for AS. Non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors and corticosteroids relieve joint pain and inflammation temporarily. Conventional DMARDs have limited efficacy on peripheral manifestation but appear to offer no benefit for axial disease [9–13]. Recently, updated treatment guidelines of the ASsessment in AS international working group (ASAS) and the European League Against Rheumatism (EULAR) recommended anti-TNF therapy for patients refractory to conventional treatments [14, 15]. Despite high cost, anti-TNF drugs were considered to be cost-effective due to demonstrated rapid onset and persistent therapeutic effect [14]. The demonstrated success of anti-TNF therapy may be due to the involvement of TNF-α in AS pathogenesis, as indicated by high TNF-α levels in inflamed sacroiliac joints of patients with AS [1, 16].

Etanercept, a dimeric human fusion protein of the extracellular ligand-binding portion of the p75 TNF receptor and the Fc component of human immunoglobulin G1 (IgG1), binds specifically to TNF-α, inhibiting its interaction with cell surface receptors [17]. Placebo-controlled clinical trials have demonstrated significant efficacy and a favourable safety profile of etanercept 25 mg twice-weekly (BIW) in patients with active AS [18–21]. Etanercept 25 mg BIW obtained regulatory approval for AS treatment in the US and the European Union. More recently, a double-blind placebo-controlled study demonstrated that 50 mg once-weekly (QW) was equivalent in efficacy and safety to the standard 25 mg BIW dose regimens in AS therapy [22]. Using data collected from the same trial, this current report focuses on the effects of both the QW and BIW dose regimens on patient-reported outcomes (PROs). In addition, the humanistic burden of AS was compared with the burden of other common medical conditions.

Patients and methods

Study design

A randomized, double-blind, placebo-controlled multicenter study was conducted for 12 weeks in 11 European countries comparing...
etanercept 50 mg QW, etanercept 25 mg BIW and placebo (3:3:1 ratio). Efficacy and safety results from this trial were published recently [22].

This trial was conducted in accordance with the ethical principles of the Declaration of Helsinki and was consistent with the guidelines for good clinical practice. All participating patients provided written informed consent. The study protocol and informed consent document were approved by each institution’s review board or independent ethics committee.

Patients

The study enrolled 361 men and women (18–70 yrs) with active AS according to the Modified New York Criteria [23] defined by a visual analog scale (VAS) for mean morning stiffness ≥30, and by at least two of the following: VAS for patient global assessment of disease activity ≥30, average of VAS for nocturnal and total pain ≥30 or Bath Ankylosing Spondylitis Functional Index (BASFI) ≥30. All VAS ranged from 0 to 100 (most severe). Stable doses of concomitant oral NSAIDS and corticosteroids administered at least 2 weeks before randomization and DMARDs (hydroxychloroquine, sulfasalazine and methotrexate) administered at least 4 weeks before randomization were allowed. Patients previously exposed to TNF-α inhibitors were excluded.

Assessment of patient-reported outcomes

PROs were assessed using EuroQOL-5D (EQ-5D), BASFI, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)-fatigue item and Medical Outcomes Short Form Questionnaire (SF-36) scores. Assessments took place at baseline, and at weeks 2, 4, 8 and 12, with the exception of SF-36, which was only administered at baseline and week 12. The generic EQ-5D questionnaire includes five dimensions of health (mobility, self care, usual activities, pain/discomfort and anxiety/depression) and is rated on three degrees of severity. A utility score was derived from published tariffs and ranged from 0 (death) to 1 (perfect health) [24]. In addition, it also contains a thermometer-like visual analogue scale (EQ-5D VAS) ranging from 0 to 100 where 100 indicates the ‘best imaginable health state’. The generic SF-36 measures general health-related QOL in the following eight domains: physical functioning, vitality, social functioning, bodily pain, mental health, general health, role limitations-physical and role limitations-emotional [25]; these subscales were scored from 0 to 100, with higher scores indicating better health status. Functional limitation was measured by the BASFI score [range: 0–100 (impaired function)] [26]. The single-item BASDAI fatigue was used to assess self-reported degree of fatigue [27]; BASDAI score ranged from 0 (no problems) to 100 (very severe problem).

Data analyses

To compare the humanistic impact of AS to that of other medical conditions, the proportion (%) of patients reporting any problem in the five dimensions of EQ-5D at baseline (pre-treatment) was compared with published figures of patients with the following medical conditions [28]: asthma, cancer, chronic obstructive pulmonary disease (COPD), depressive symptoms, diabetes and heart disease. Similarly, mean SF-36 scores at baseline (pre-treatment) were compared with the US national norms and to previously reported scores for congestive heart failure (CHF), diabetes, hypertension and clinical depression [25]. No statistical analysis was conducted on these comparisons.

Statistical analyses

The modified intention-to-treat (mITT) population, defined as all subjects who received at least one dose of placebo or etanercept, was the primary population. The last-observation carried forward (LOCF) method was used for imputing missing data. Baseline characteristics were analysed using one-way analysis of variance (ANOVA) for continuous variables, and Fisher’s exact test for categorical variables. At each time point in the trial, change from baseline in EQ-5D VAS, EQ-5D utility, SF-36, BASFI and BASDAI-fatigue scores were computed. Pair-wise comparison of each treatment group on change from baseline was made using analysis of covariance (ANCOVA) adjusting for baseline score, country, prior use of DMARDs and treatment. Lastly, the proportion of patients achieving values of minimum clinically important difference (MCID) identifying improvement at week 12 was compared by treatment group for BASFI, EQ-5D utility score and the eight SF-36 subscales. Changes of 7 points for BASFI [29], 0.05 for the EQ-5D utility [30] and 5–10 points in the SF-36 subscales [25] are considered to reflect MCID.

Results

All but 5 of the 361 patients enrolled were randomized to study groups; these 356 patients made up the mITT population. Of these, 321 (90%) completed 12 weeks of treatment. Most patients were men, and their baseline characteristics, disease activity and use of medication did not differ significantly (Table 1).

### Quality-of-life in patients with AS at baseline

 Patients with AS reported problems in all EQ-5D dimensions (Table 2). The proportion of patients reporting problems was much higher than with other common medical conditions (asthma, heart disease, cancer, diabetes, COPD and depressive symptoms). In particular, almost all patients with AS reported pain or discomfort (99%), and more than three out of four patients indicated problems in mobility and with performing usual activities. Almost two-thirds of the patients reported problems with anxiety or depression.

Mean SF-36 scores for patients with AS were lower than the US national norms for all SF-36 components (Table 3). Confirming results from the EQ-5D, the SF-36 scores for patients with AS were comparable or lower than most other medical conditions (hypertension, CHF, diabetes and clinical depression). The difference in SF-36 scores between patients with AS and the US norms or other chronic conditions was most pronounced in the domains of role limitations-physical, physical functioning, bodily pain and general health. Scores for social functioning, vitality and mental health were similar to those for clinical depression but lower than for CHF, diabetes and hypertension, indicating the debilitating psychosocial dimension of AS.
Etanercept once-weekly improves patient-reported outcomes

**TABLE 2. Percent of patients reporting any problem in EQ-5D dimensions: AS baseline (current study) compared with patients with other medical conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>AS Baseline</th>
<th>Asthma*</th>
<th>Cancer*</th>
<th>COPD*</th>
<th>Depressive symptoms*</th>
<th>Diabetes*</th>
<th>Heart disease*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility</td>
<td>79.8</td>
<td>26.7</td>
<td>40.0</td>
<td>40.0</td>
<td>17.2</td>
<td>55.2</td>
<td>37.5</td>
</tr>
<tr>
<td>Usual activities</td>
<td>89.9</td>
<td>26.7</td>
<td>40.0</td>
<td>46.7</td>
<td>18.8</td>
<td>44.8</td>
<td>56.3</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>64.6</td>
<td>33.3</td>
<td>30.0</td>
<td>40.0</td>
<td>40.9</td>
<td>46.4</td>
<td>41.7</td>
</tr>
<tr>
<td>Self care</td>
<td>57.0</td>
<td>3.3</td>
<td>10.0</td>
<td>0.0</td>
<td>3.3</td>
<td>13.8</td>
<td>6.3</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td>99.2</td>
<td>56.7</td>
<td>50.0</td>
<td>66.7</td>
<td>46.7</td>
<td>63.8</td>
<td>81.3</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; EQ-5D, EuroQOL-5D. *From Johnson and Coons [28].

**TABLE 3. Mean (baseline) SF-36 Scores: AS patients compared with patients with other medical conditions**

<table>
<thead>
<tr>
<th>Domain</th>
<th>AS US norms*</th>
<th>CHF*</th>
<th>Diabetes*</th>
<th>Hypertension*</th>
<th>Clinical depression*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>45.9</td>
<td>84.2</td>
<td>47.5</td>
<td>67.7</td>
<td>73.4</td>
</tr>
<tr>
<td>Vitality</td>
<td>39.4</td>
<td>60.9</td>
<td>44.3</td>
<td>55.7</td>
<td>58.3</td>
</tr>
<tr>
<td>Social functioning</td>
<td>52.3</td>
<td>83.3</td>
<td>71.3</td>
<td>82.0</td>
<td>86.7</td>
</tr>
<tr>
<td>Mental health</td>
<td>58.6</td>
<td>74.7</td>
<td>74.7</td>
<td>76.7</td>
<td>77.9</td>
</tr>
<tr>
<td>Role limitations-physical</td>
<td>23.5</td>
<td>81.0</td>
<td>34.8</td>
<td>56.8</td>
<td>62.0</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>30.2</td>
<td>75.2</td>
<td>62.7</td>
<td>68.5</td>
<td>72.3</td>
</tr>
<tr>
<td>Role limitations-emotional</td>
<td>51.2</td>
<td>81.3</td>
<td>63.7</td>
<td>75.6</td>
<td>76.7</td>
</tr>
<tr>
<td>General health</td>
<td>53.7</td>
<td>72.0</td>
<td>47.1</td>
<td>56.1</td>
<td>63.3</td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; SF-36, Medical Outcomes Short Form Questionnaire. *From Ware et al. [25].

**Quality of life in patients with AS following etanercept treatment**

Figures 1 and 2 show the change from baseline in EQ-5D VAS and EQ-5D utility scores over 12 weeks, respectively. The EQ-5D VAS score improvement for etanercept 25 mg BIW and etanercept 50 mg QW was significantly greater than placebo from week 2 to week 12 (Fig. 1). The improvement was comparable between the two etanercept groups, etanercept 50 mg QW (filled circle) and etanercept 25 mg BIW (filled triangle), were compared with placebo (blank square). Significant difference between etanercept 50 mg QW and placebo at all time points: \( P < 0.001 \) (†), \( P < 0.0001 \) (*). Significant difference between etanercept 25 mg BIW and placebo at all time points: \( P = 0.001 \) (‡), \( P < 0.05 \) (§), \( P < 0.0001 \) (¶) and \( P < 0.001 \) (‖).

**FIG. 1.** Mean improvement from baseline in EQ-5D VAS score. Two etanercept regimens, etanercept 50 mg QW (filled circle) and etanercept 25 mg BIW (filled triangle), were compared with placebo (blank square). Significant difference between etanercept 50 mg QW and placebo at all time points: \( P < 0.001 \) (†), \( P < 0.0001 \) (*). Significant difference between etanercept 25 mg BIW and placebo at all time points: \( P = 0.001 \) (‡), \( P < 0.05 \) (§), \( P < 0.0001 \) (¶) and \( P < 0.001 \) (‖).

**FIG. 2.** Mean improvement from baseline in EQ-5D utility score. Two etanercept groups, etanercept 50 mg QW (filled circle) and etanercept 25 mg BIW (filled triangle), were compared with placebo (blank square). Significant difference between etanercept 50 mg QW and placebo at all time points: \( P < 0.05 \) (†), \( P < 0.001 \) (*). Significant difference between etanercept 25 mg BIW and placebo at week 8 and 12: \( P < 0.001 \) (‡) and \( P < 0.01 \) (§), respectively.

**FIG. 3.** Mean SF-36 scores pre- and post-treatment. Baseline (pre-treatment) SF-36 scores were measured for the following treatment groups: etanercept 50 mg QW (black bars), etanercept 25 mg BIW (grey bars) and placebo (white bars). Improvement in SF-36 scores following treatment with etanercept or placebo was also reported (dotted bars). Significant difference between etanercept 50 mg QW and placebo: \( P < 0.001 \) (†), \( P < 0.01 \) (‡), \( P < 0.001 \) (§), and \( P = 0.0001 \) (**). Significant difference between etanercept 25 mg BIW and placebo: \( P < 0.01 \) (†), \( P = 0.0001 \) (‡), \( P < 0.001 \) (§), \( P < 0.05 \) (¶) and \( P < 0.001 \) (‖). Significant difference between etanercept 50 mg QW and etanercept 25 mg BIW for vitality \( P = 0.03 \) (#), mental health \( P = 0.02 \) (††), and general health \( P = 0.001 \) (‡‡). PF, physical functioning; RP, role-physical; VT, vitality; BP, bodily pain; RE, role-emotional; MH, mental health; SF, social functioning; GH, general health.
subscases of mental health ($P = 0.02$), vitality ($P = 0.03$) and general health ($P = 0.001$).

Improvement in BASFI was significantly greater for the two etanercept groups compared with placebo at all time points, except at week 2 for etanercept 25 mg BIW (Fig. 4). There was no significant difference between the two etanercept groups.

Fatigue is a major symptom of AS and can be appropriately measured with the BASDAI fatigue item [31]. By week 8, mean improvement from baseline for both etanercept groups was significantly higher than that for the placebo group (Fig. 5). Improvement was comparable with no significant differences between etanercept 50 mg QW and etanercept 25 mg BIW.

The MCID was assessed for BASFI, EQ-5D and SF-36 scores at week 12 (Fig. 6). The proportions of patients achieving BASFI MCID for etanercept 25 mg BIW and 50 mg QW (74 and 78%, respectively) were significantly greater than those receiving placebo (49%; $P < 0.001$). Two-thirds of the patients receiving etanercept reported clinically important improvements in EQ-5D utility whereas half of the placebo group reported improvements ($P < 0.01$ for etanercept 50 mg QW). For SF-36, a greater proportion of patients receiving etanercept 25 mg BIW (31–71%) or etanercept 50 mg QW (41–72%) met or exceeded MCID than the placebo group (24–41%) in many of the subscales. The subscales with the lowest proportion of patients achieving MCID were role limitations-emotional and mental health, and subscales with the highest proportions were bodily pain and social functioning.

**Discussion**

Previous studies have consistently demonstrated that etanercept 25 mg BIW significantly improved PROs in patients with active AS [7, 21, 32]. The current study extended these findings, providing additional evidence that the more convenient etanercept 50 mg QW dose regimen is as effective as etanercept 25 mg BIW in improving PROs. First, this study showed that the humanistic burden of active AS is similar to or, in most health dimensions, worse than other common chronic conditions (CHF, diabetes and hypertension). Second, treatment with etanercept resulted in significant improvement of all PRO measures, including physical function, fatigue, pain, psychosocial domains and general health status. PRO improvements were comparable between the two etanercept dose regimens, complementing the clinical equivalence and safety findings from our earlier report [22]. This finding mirrors a separate study of the effects of etanercept in the treatment of RA, where the 25 mg BIW and 50 mg QW dose regimens also displayed similar efficacy and safety profiles [33].

The pre-treatment data in the current study revealed marked decrements in domains related to physical aspects measured by the EQ-5D and SF-36; a high degree of pain and low physical function were reported by patients with AS. This is consistent with previous studies reporting a deterioration of functional status in patients with active AS, where physical domains being consistently the most affected [6–8, 34, 35]. Compared with other severe medical conditions (cancer and heart disease), QOL impairment in AS was more pronounced, despite the younger age of the AS patient population from the current study compared with the age of patients with other conditions in the comparison groups (mean age: 52.3–67 yrs [25, 28]). A similar magnitude of physical impairment to that observed in the current study was reported earlier by Davis et al. [7] who investigated two independent samples of US and multinational patients with AS of comparable disease duration; both the current study and the one by Davis et al. were clinical drug trials.

Although reduced physical functioning is well recognized in patients with active AS [6–8], the impact on social and mental health aspects has not received as much attention. The limited literature available suggests that the disease impact on
psychosocial dimensions is less marked than the physical aspects. Nevertheless, psychosocial domains of health-related QOL are considerably diminished compared with that in the general population [6-8]. The current study reported a substantial decrease in SF-36 psychosocial domains, with scores ranging from 51.2 to 58.8, compared with 74.7 to 83.3 for the general population on mental health, social functioning and role limitations-emotional aspects. In addition, scores from studies unrelated to drug trials indicate that psychosocial aspects appear to be affected to a similar degree across AS patients with various levels of physical ability [6, 8, 34].

Anti-TNF therapy has proven to be effective in the treatment of AS. A Norwegian longitudinal, observational study demonstrated improved SF-36 scores following infliximab or etanercept therapy for 3–6 months, supporting the use of anti-TNF drugs to treat patients with AS [35]. The current study demonstrated improved PROs after etanercept therapy, with high proportions achieving clinically meaningful improvements in PRO measures. Etanercept 25 mg BIW and 30 mg QW improved BASFI scores by 43 and 47.4%, respectively. This is consistent with previous findings from a 54-week, open, observational study that shows 42% improvement in BASFI after etanercept 25 mg BIW [32], and similar (30–51% improvement) to other etanercept studies with varying length of follow-up [18–21]. Improvement of the BASDAI fatigue item observed with etanercept 25 mg (40.8%) and 50 mg (48.8%), was also similar to improvements reported in earlier trials [19, 32].

Similar significant improvements in all SF-36 domains were reported in this study, confirming previous findings from a US clinical trial using two independent samples of US and multinational patients [7]. The most affected SF-36 components (role limitations-physical and bodily pain) had the greatest improvement with both etanercept dose regimens. Interestingly, after etanercept treatment, SF-36 scores approached values described for other chronic conditions, and displayed the smallest gap to the US norms in the domains of vitality and mental health (vitality: 54.2 and 57.4 for etanercept 25 mg and 50 mg vs 60.9 for US norms; mental health: 68.5 and 71.1 for etanercept 25 mg and 50 mg vs 74.7 for US norms). BASDAI fatigue and SF-36 vitality scores were associated with self-reported measures of mental health and disease activity [36], suggesting that improvement of these parameters reflects a reduction of disease activity. Consistently, an earlier report demonstrated a significant improvement in clinical outcomes as measured by ASAS20 response in the same patient population as the current study [22].

Limitations of the current study should be considered. The latest evaluation time-point was at week 12, corresponding with the end of treatment. Although this duration fits within the recommended time interval for the assessment of a treatment response in the ASAS/EULAR recommendations [14] and the BSR guidelines [37], a longer follow-up period may be required to evaluate sustained improvement in PROs. However, given that previous AS trials with longer term monitoring up to 160 weeks demonstrated sustained improvement in ASAS 20 response [38, 39] and PROs [40], it is likely that improvement can be sustained. Limitations may apply to the instruments used to measure PROs. Concerns about the reliability of EQ-5D utility values have been raised [41]. However, it was suggested that EQ-5D limitations could be overcome by the use of the VAS index [28]. This analysis, based on a wide panel of instruments, consistently showed impaired QOL in AS and improvement after etanercept therapy. Moreover, BASFI and BASDAI have been shown to have high levels of reliability, validity and responsiveness to therapy [42]. Strong evidence of the generic SF-36 questionnaire responsiveness to drug therapy has also been demonstrated [42]. BASDAI fatigue item has been shown to reflect QOL, and is significantly associated with the level of disease activity, functional ability and mental health status [31, 36].

In conclusion, this study confirms earlier findings that active AS imposes a significant humanistic burden, and treatment with etanercept is associated with significant improvements in PROs. Etanercept 50 mg QW was equally effective as the standard 25 mg BIW dose regimen at improving PROs. Given the convenience of once-weekly injection, the use of 50 mg QW to treat patients with active AS is supported.

### Rheumatology key messages

- Etanercept improves PROs in patients with active AS.
- Etanercept 50 mg QW and 25 mg BIW are equally effective at improving PROs.

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