Patient-reported Outcomes in a Randomized Trial of Etanercept in Psoriatic Arthritis

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ABSTRACT. Objective. To evaluate the effects of etanercept treatment on patient-reported outcomes (PRO) in patients with psoriatic arthritis (PsA).

Methods. A 24-week double-blind comparison to placebo was followed by a 48-week open-label phase in which all eligible patients received etanercept. PRO were measured using the Stanford Health Assessment Questionnaire Disability Index (HAQ-DI), the Medical Outcomes Study Short-Form (SF-36), the EQ-5D visual analog scale (VAS), and the American College of Rheumatology (ACR) patient pain assessment.

Results. Beginning at Week 4 and continuing through Week 24 of double-blind treatment, patients treated with etanercept had significantly higher mean percentage improvement in HAQ-DI relative to baseline than patients given placebo (53.6% vs 6.4% at Week 24; p < 0.001). After 48 weeks of open-label treatment with etanercept, the mean percentage change from study baseline was 52.8% for the original etanercept group and 46.9% for the original placebo group, with 41.2% of patients overall achieving a HAQ-DI of 0. Mean changes relative to baseline for SF-36 physical component summary scores, EQ-5D VAS, and ACR pain assessment were also significant in the double-blind period for etanercept compared with placebo (p < 0.001 for all 3 measures). Patients taking placebo achieved similar improvements once they began treatment with etanercept in the open-label period.

Conclusion. Patients with PsA treated with etanercept reported significant improvements in physical function that were almost 10 times the improvement seen with placebo and were maintained for up to 2 years. Almost half of patients treated with etanercept reported no disability by the end of the study. (First Release April 15 2010; J Rheumatol 2010;37:1221–7; doi:10.3899/jrheum.091093)

Key Indexing Terms:
PSORIATIC ARTHRITIS QUALITY OF LIFE DOUBLE-BLIND METHOD ETANERCEPT PATIENT OUTCOMES ASSESSMENT
limited to a few joints, distal interphalangeal (DIP) joint involvement, axial involvement, enthesitis, dactylitis, and radiographic features such as pencil-in-cup deformity, gross osteolysis, joint space widening, ankylosis, juxtaarticular periostitis, shaft periostitis, and tuft resorption. Many patients have erosive disease, physical limitations, and work-related disability. Patients with PsA who were pregnant or breastfeeding, as well as those with diabetes mellitus requiring insulin, uncompensated congestive heart failure, PsA with active arthritis and an inadequate response to nonsteroidal antiinflammatory drugs (NSAID) therapy, and history of cancer other than resected cutaneous basal and squamous cell carcinoma or in situ cervical cancer. All patients provided written informed consent before study entry. Disease-modifying antirheumatic drugs (DMARD) were not permitted during the study. Methotrexate, NSAID, corticosteroids, and topical therapies were permitted if stable doses had been achieved before study entry.

Study drug. The study medication (etanercept or placebo) was supplied as sterile, lyophilized powder in vials and was reconstituted by site personnel not involved in data collection for the study (double-blind phase) or by patients (open-label phase). Study medication was administered twice weekly by subcutaneous injection either by the patient or a designated person. Change in dose of study drug was not permitted. Interruptions of up to 1 week (i.e., 2 doses) were permitted in the case of grade 3 or 4 toxicity, defined according to the National Institutes of Health, National Cancer Institute Common Toxicity Criteria (version 2.0). Recurrence of the same grade 3 or 4 toxicity necessitated discontinuation of treatment.

Clinical and radiographic assessments. Efficacy of treatment of arthritis was measured by the percentages of patients meeting the American College of Rheumatology 20% response criteria (ACR20), as modified for PsA by inclusion of DIP and carpometacarpal (CMC) joints, and the Psoriatic Arthritis Response Criteria (PsARC). Response to treatment of psoriasis was based on the dermatologist’s global assessment of target lesions and the percentage of patients achieving 50% improvement on the Psoriasis Area and Severity Index (PASI 50). Articular damage was assessed using total Sharp scores of radiographic images of the hands and wrists; Sharp scores were modified for PsA by inclusion of the DIP and CMC joints.

Patient-reported outcomes. Patient-reported outcomes included the HAQ-DI, the SF-36, the EQ-5D visual analog scale (VAS) (i.e., feeling thermometer1) and the ACR patient pain assessment. The HAQ-DI comprises a series of 20 questions in 8 domains (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities) related to physical functioning as required for usual daily activities. The HAQ-DI score is a composite ranging from 0 to 3, with lower scores indicating better outcomes.

SF-36 scores are based on a 36-item questionnaire measuring 4 physical function domains (physical functioning, role limitations attributable to physical problems, bodily pain, and general health) and 4 mental function domains (vitality, social functioning, role limitations attributable to emotional problems, and mental health). Scores for each domain ranged from 0 to 100, with higher scores indicating better functional status. SF-36 scores were normalized according to the method of Ware and colleagues, which uses data from the general US population, in which 50 points represents the US norm and 10 points represents 1 SD unit. The EQ-5D VAS evaluated the patient’s health state using a vertical VAS ranging from 0 (worst health) to 100 (best health). The ACR patient pain assessment used a horizontal Likert scale, with 0 corresponding to “normal” and 10 corresponding to “most abnormal.” All PRO were measured at baseline and at 4, 12, and 24 weeks during the double-blind period; every 12 weeks during the maintenance period; and every 12 weeks during the 48-week open-label period. To gauge patient assessment of change, patients were asked to rate the importance of their change in physical function on a 7-point scale (1 = not at all important; 7 = extremely important).

Statistical analysis. Treatment group comparisons were based on scores and percentage change for the HAQ-DI and ACR pain scale, as well as normalized scores and change from baseline for the EQ-5D VAS and SF-36 physical component and mental component summary scores. The percentage improvement from baseline was defined as the percentage change in the direction of improvement, that is, lower HAQ-DI and ACR pain scores and higher SF-36 and EQ-5D VAS scores. Hypothesis testing of treatment comparisons was based on a 2-sided Wilcoxon rank-sum test. No adjustments were made for multiple comparisons. In the double-blind treatment period, missing data were imputed using the method of last observation carried forward. In the open-label phase, analyses were based on observed patients; no imputation was performed.
RESULTS

Patients. A total of 205 patients were randomized in the double-blind phase of the study: 101 were randomly assigned to etanercept and 104 were randomly assigned to placebo. Of these, 169 (88 originally assigned to etanercept; 81 originally assigned to placebo) elected to participate in the open-label study. The 2 randomized groups were well balanced at baseline in terms of demographic and disease characteristics. The median time since diagnosis of PsA was 6 to 7 years, the median age was approximately 47 years, and approximately 90% of patients were white. The placebo group had a slight predominance of women (55%), while the etanercept group had a slight predominance of men (57%). Patients in the etanercept group had more severe radiographic disease at baseline than patients in the placebo group. Most patients (84%) had polyarticular arthritis. The 169 patients who elected to participate in the open-label study had baseline demographic characteristics and disease history similar to those in the overall cohort of 205 randomized patients, as did the 148 patients who completed the 48-week open-label period. Mean (range) total exposure to etanercept was 560.1 (71–744) days for patients originally randomized to etanercept and 315.5 (1–361) days for patients originally randomized to placebo.

Clinical efficacy. Detailed analyses of clinical and radiographic results and safety measurements in this study were reported elsewhere. During the double-blind phase of the study, significantly more patients randomly assigned to etanercept responded, as determined by ACR20 criteria (p < 0.0001), PsARC (p < 0.001), and PASI 50 criteria (p < 0.001) than did patients randomly assigned to placebo. Radiographic disease progression was inhibited in the etanercept group compared with the placebo group at 12 months (p = 0.0001). Within 12 weeks of starting etanercept in the open-label phase of the study, patients originally assigned to placebo achieved comparable clinical results to patients initially randomized to etanercept treatment, and results were maintained in both groups throughout the open-label phase.

Patient-reported outcomes. Mean HAQ-DI scores before treatment were 1.1 units in both groups. Within 4 weeks of initiating treatment, HAQ-DI scores were significantly improved in patients receiving etanercept compared with scores in patients receiving placebo. Week 4 scores were 0.7 units for etanercept and 1.0 unit for placebo, corresponding to percentage improvements of 35.1% and 8.0%, respectively (p < 0.001; Figure 1A). Continued improvement in HAQ-DI scores was observed with additional treatment (Table 1), reaching mean percentage changes of 53.5% in the etanercept group by Week 12, compared with a 6.3% change for patients in the placebo group (p < 0.001; Figure 1A). Improvements achieved at Week 12 were maintained at Week 24 in both groups (Table 1 and Figure 1A). At the start of the open-label phase, mean HAQ-DI scores were 0.4 units in the etanercept group and 1.0 unit in the placebo group. During the open-label phase, patients originally assigned to etanercept therapy maintained or improved their HAQ-DI scores from the double-blind period (Figure 1B) with a 52.8% improvement from original study baseline at Week 48. Patients originally assigned to placebo demonstrated improvement in their HAQ-DI scores within 12 weeks of initiating treatment with etanercept, reaching a mean score of 0.7 at Week 12 (36.2% improvement from original study baseline). Continued improvement was

Figure 1. Mean percentage improvement in HAQ-DI scores. All data represent the mean percentage change from baseline and error bars are standard error. A. Double-blind phase: Results are based on last observation carried forward imputation; mean baseline scores were 1.1 (0.1) units for both treatment groups. B. Open-label phase: Results are based on the observed population at each time; baseline scores were 1.0 (0.1) units for patients taking placebo- etanercept and 0.4 (0.1) units for patients taking etanercept- etanercept. HAQ-DI: Health Assessment Questionnaire-Disability Index.
observed, with patients achieving a mean score of 0.6, corresponding to a 46.9% improvement at Week 48 (Table 1 and Figure 1B).

At the end of the double-blind phase, the percentage of patients with a HAQ-DI score of 0, indicating no disability on any of the 8 domains of the HAQ-DI, was higher among patients randomized to etanercept than among patients randomized to placebo (38% vs 7%; Figure 2). After 48 weeks of open-label treatment, 53% of patients continuously treated with etanercept and 29% of patients originally assigned to placebo reported a HAQ-DI of 0.

Before treatment, mean SF-36 physical component summary scores for patients in both treatment arms were below the US norm of 50 units (etanercept, 35.8 units; placebo, 35.7 units). During the double-blind phase, the mean improvement from baseline in SF-36 physical component summary scores was significantly greater for patients in the etanercept group than for patients in the placebo group as early as Week 4 (5.8 units vs 0.5 units; p < 0.001) and at all later assessment times (Figure 3A). By Week 24 of the double-blind phase, SF-36 scores had improved by 9.3 units in the etanercept group vs 0.7 units in the placebo group (p < 0.001; Figure 3A) to scores of 45.1 and 36.4, respectively (Table 1). SF-36 physical component summary scores at open-label baseline were 46.4 for patients originally assigned to etanercept and 36.8 for patients originally assigned to placebo. During the open-label phase, patients originally assigned to etanercept therapy maintained or improved their SF-36 physical component summary scores from the double-blind period (Table 1 and Figure 3B).

Patients originally assigned to placebo improved their physical component summary scores by 8.3 units within 12 weeks of starting treatment with etanercept, and by the end of the 48-week open-label study period, these patients achieved a mean score of 44.1 units (Table 1).

Mean SF-36 mental component summary scores at original study baseline were at or approaching the US norm of 50 units in both treatment groups (etanercept, 50.9 units; placebo, 48.4 units; Table 1). As expected, mean changes in SF-36 mental component summary scores were of lower magnitude than the changes observed for SF-36 physical component summary scores in both groups of patients and in both treatment periods (Table 1). After 24 weeks of blinded therapy, changes of 2.7 units and –0.1 units (p = 0.062) were observed in the etanercept and placebo groups, respectively. Mean scores at the start of the open-label phase were 53.7 units for patients originally assigned to etanercept and 49.1 units for patients originally assigned to placebo (Table 1). Improvements from the original study baseline of 1.6 units and 0.6 units, in the etanercept-etanercept and placebo

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### Table 1. Mean scores for patient-reported outcomes during the double-blind and open-label treatment periods.

<table>
<thead>
<tr>
<th>Time</th>
<th>HAQ-DI Mean (SE)</th>
<th>EQ-5D Mean (SE)</th>
<th>SF-36 PCS Mean (SE)</th>
<th>SF-36 MCS Mean (SE)</th>
<th>ACR Pain Mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>placebo</td>
<td>etanercept</td>
<td>placebo</td>
<td>etanercept</td>
<td>placebo</td>
</tr>
<tr>
<td>Baseline</td>
<td>1.1 (0.1)</td>
<td>1.1 (0.1)</td>
<td>62.0 (2.2)</td>
<td>64.7 (2.0)</td>
<td>35.7 (0.9)</td>
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<tr>
<td>Week 24 of DB</td>
<td>1.0 (0.1)</td>
<td>0.5 (0.1)</td>
<td>64.2 (2.2)</td>
<td>79.0 (1.7)</td>
<td>36.4 (1.0)</td>
</tr>
<tr>
<td>Start of OL</td>
<td>1.0 (0.1)</td>
<td>0.4 (0.1)</td>
<td>63.1 (2.5)</td>
<td>81.6 (1.5)</td>
<td>36.8 (1.1)</td>
</tr>
<tr>
<td>Week 12</td>
<td>0.7 (0.1)</td>
<td>0.5 (0.1)</td>
<td>76.2 (2.0)</td>
<td>81.7 (1.7)</td>
<td>39.9 (1.2)</td>
</tr>
<tr>
<td>Week 24</td>
<td>0.6 (0.1)</td>
<td>0.4 (0.1)</td>
<td>77.7 (2.0)</td>
<td>82.1 (1.6)</td>
<td>44.4 (1.1)</td>
</tr>
<tr>
<td>Week 36</td>
<td>0.6 (0.1)</td>
<td>0.4 (0.1)</td>
<td>76.7 (2.0)</td>
<td>82.6 (1.7)</td>
<td>44.2 (1.2)</td>
</tr>
<tr>
<td>Week 48</td>
<td>0.6 (0.1)</td>
<td>0.4 (0.1)</td>
<td>77.6 (1.9)</td>
<td>83.6 (1.5)</td>
<td>44.1 (1.3)</td>
</tr>
</tbody>
</table>

HAQ-DI: Health Assessment Questionnaire Disability Index; EQ-5D: EuroQol self-report questionnaire; SF-36 PCS: Short-Form 36 physical component summary; SF-36 MCS: Short-Form 36 mental component summary; ACR Pain: American College of Rheumatology patient pain assessment.

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**Figure 2.** Percentage of patients with no disability according to HAQ-DI, defined as a HAQ-DI score of 0. Results are based on last observation carried forward imputation in the double-blind phase and on the observed population at each time in the open-label phase. Baseline refers to data obtained at study entry. HAQ-DI: Health Assessment Questionnaire Disability Index; DB: double-blind phase; OL: open-label phase.
etanercept groups, respectively, occurred after 48 weeks of open-label treatment.

Patients randomized to etanercept reported better global health according to the EQ-5D VAS after 24 weeks of blinded therapy than did patients randomized to placebo (Table 1). The mean change from baseline to 24 weeks was 14.3 units in patients taking etanercept and 2.1 units in patients taking placebo (p < 0.001). Patients taking etanercept main-
The functional improvement in patients with PsA following etanercept treatment observed in our study is consistent with improvement observed in a Phase 2 study of etanercept treatment in patients with PsA. In our study, patients receiving etanercept experienced rapid and sustained improvements in HAQ-DI and SF-36 physical component summary scores that were maintained throughout the treatment period. Mean SF-36 physical component summary scores were well below the US norm of 50 units at baseline and were improved to levels that approached the US norm with etanercept therapy. At baseline our patient population had a mean SF-36 mental component summary score that was at normal levels for the US population. Thus, as expected, SF-36 mental component summary scores did not significantly improve with etanercept treatment over the course of our study.

In addition to improving functional ability in patients with PsA, etanercept has been shown to reduce patient-reported pain. In a randomized clinical trial of etanercept in patients with PsA and psoriasis, patient-reported pain was eliminated in 17% of patients treated with etanercept, while patients who received placebo reported no pain cessation. In our study, patients treated with etanercept in the double-blind period experienced substantial improvement in self-reported pain compared with patients receiving placebo. When patients in the placebo group were treated with etanercept in the open-label period, improvement in patient-reported pain was evident by the first assessment and continued throughout the duration of our study. The improvement in physical function and reduction in pain may have contributed to the steady and consistent improvement in patient-perceived health state, as measured by EQ-5D, in patients treated with etanercept over the course of our study.

Patient-reported outcomes are increasingly important in assisting physicians in making appropriate treatment decisions for patients with PsA. Although the instruments used in this analysis were not specifically developed for patients with PsA, they have been shown to be responsive, discriminative, and relatively easy to use. Moreover, while no single instrument can accurately quantify the total effect of disease at present, the use of multiple patient self-reported instruments may help to determine the functional and psychosocial ramifications of PsA. In our study, we have shown that the extended treatment with etanercept in patients with PsA is not only effective with respect to traditional physician-based assessments but also according to assessments performed by the patients themselves.

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