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Six-Month Results of a Double-Blind, Placebo-Controlled Trial of Etanercept Treatment in Patients With Active Ankylosing Spondylitis

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Objective. **There is increasing evidence that tumor necrosis factor α (TNFα) is centrally involved in the pathogenesis of ankylosing spondylitis (AS) and other spondylarthritides. This study was designed to investigate the efficacy of anti-TNFα therapy with etanercept, a 75-kd receptor fusion protein, in active AS.**

Methods. **This multicenter trial had 2 phases: an initial placebo-controlled period of 6 weeks' duration and an observational phase lasting 24 weeks. Thirty patients with active AS were included. They were randomized into 2 groups, which received either etanercept (25 mg twice weekly) (n = 14) or placebo (n = 16) for 6 weeks. Then both groups were treated with etanercept. Nonsteroidal antiinflammatory drug (NSAID) treatment could be continued, but disease-modifying antirheumatic drugs (DMARDs) and steroids had to be withdrawn prior to the study. All patients received etanercept for a total of 12 weeks and were followed up for at least 24 weeks. The Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index, Bath AS Metrology Index, pain level on a numeric rating scale, quality of life by the Short Form 36, and C-reactive protein (CRP) level were assessed. The primary outcome parameter was a ≥50% improvement in the BASDAI.**

Results. **Treatment with etanercept resulted in at least a 50% regression of disease activity in 57% of these patients at week 6, versus 6% of the placebo-treated patients ($P = 0.004$). After the placebo-treated patients switched to etanercept, 56% improved. The mean ± SD BASDAI improved from 6.5 ± 1.2 at baseline to 3.5 ± 1.9 at week 6 in the etanercept group, with no improvement in the placebo group ($P = 0.003$ between groups). Similarly, pain, function, mobility, and quality of life improved with etanercept but not with placebo at week 6 ($P < 0.05$). Mean CRP levels decreased significantly with etanercept but not with placebo ($P = 0.001$). There was ongoing improvement in all parameters in both groups until week 12 and week 18, respectively (i.e., throughout the period of etanercept treatment). Disease relapses occurred a mean ± SD of 6.2 ± 3.0 weeks after cessation of etanercept. No severe adverse events, including major infections, were observed during the trial.**

Conclusion. **This study shows that on a short-term basis (3 months), treatment with etanercept is clearly efficacious in patients with active AS who are receiving NSAID therapy but not DMARDs or steroids. After cessation of therapy, almost all patients experienced a relapse within a few weeks. Thus, it seems probable that etanercept must be administered continuously in most AS patients to achieve permanent inhibition of the inflammatory process.**

Ankylosing spondylitis (AS), the prototype of the spondylarthritides (SpA), is a chronic inflammatory rheumatic disease. In the past, the prevalence of SpA has been underestimated (1); more recently, the prevalence of the group of SpA as a whole has been calculated

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to be 0.5–1.9% (2), similar to that of rheumatoid arthritis (RA). The interaction between a strong genetic component, mainly represented by certain HLA–B27 subtypes (3), and bacteria seems to be crucial for the pathogenesis of AS (4). Inflammation of the sacroiliac joints, the entheses (5), and the spine (6) is most characteristic. The disease, which affects both sexes, usually starting in the second or third decade of life, is still underdiagnosed (7,8). Like RA, AS causes significant disability in a substantial proportion of patients (7). However, because AS usually begins at a younger age, patients have the disease for a longer period of time, and the direct and indirect socioeconomic costs are thus considerable (8,9).

In contrast to RA, there are only a few studies on treatment with disease-modifying antirheumatic drugs (DMARDs) in AS. No DMARD has been shown to be clearly effective in axial disease. Sulfasalazine has limited efficacy in patients with peripheral arthritis and possibly in early disease stages (10). No studies have provided convincing evidence of efficacy of methotrexate in AS. Currently, therapy for AS consists mainly of nonsteroidal antiinflammatory drugs (NSAIDs) and physiotherapy. In contrast to RA, systemic corticosteroids are effective only in selected patients. Patients with severe AS may have to be treated with phenylbutazone and opioids for pain relief. Thus, treatment options for AS are limited, and the quality of life is reduced in a large percentage of patients (11). Accordingly, therapy for severe AS is considered an unmet medical need.

There is evidence that tumor necrosis factor α (TNFα) is expressed in inflamed sacroiliac joints of AS patients (12). Anti-TNFα therapy with etanercept (Enbrel; Immunex, Seattle, WA), a dimeric fusion protein of the human 75-kd (p75) TNF receptor linked to the Fc portion of human IgG1, has been shown to be highly effective in RA (13). RA, however, is pathogenetically distinct from AS. Anti-TNFα therapy with infliximab is approved for Crohn's disease, which is closely linked to AS (14). As recently shown by our group in an open trial (15,16) and in a randomized trial (17), anti-TNFα therapy is also very efficacious in active AS.

Etanercept was recently found to be beneficial in SpA, in terms of both clinical and magnetic resonance imaging (MRI) findings, in an open study with 10 patients (18). In a randomized controlled trial of etanercept in 40 AS patients who were allowed to continue treatment with NSAIDs, DMARDs, and steroids, improvement of disease activity and other parameters was reported (19). The present study was performed to investigate the efficacy of etanercept in the treatment of patients with active AS who are not taking DMARDs or steroids and to compare the 2 anti-TNF agents, using the same outcome variables.

PATIENTS AND METHODS

Patients and study protocol. This randomized, placebo-controlled, multicenter trial was designed to investigate whether the administration of etanercept (25 mg twice weekly) is effective in the treatment of active AS. Only patients who fulfilled the modified New York criteria for AS (20) and had active disease as defined by a Bath AS Disease Activity Index (BASDAI) (21) of $\geq$4 and spinal pain of $\geq$4 on a 0–10 numeric rating scale were included. Patients were excluded if they had had active tuberculosis within the previous 3 years, a serious infection within the previous 2 months, lymphoproliferative disease or other malignancies within the previous 5 years, multiple sclerosis or a related disorder, or current signs or symptoms of severe disease. The study was approved by the local ethics committees, and patients gave written informed consent before participation.

DMARDs and oral corticosteroids were withdrawn at least 4 weeks before screening. Patients were allowed to continue treatment with NSAIDs; no increase over the baseline dosage was permitted, but a reduction was allowable and had to be recorded.

Of 49 patients screened, 16 were not included because of low disease activity, widespread ankylosis, and/or relevant comorbidity such as previous infection. Initials and sex of the 33 remaining patients were reported to a central independent registration office by fax. Patients were randomly allocated to one of the treatment groups. The pharmacist at each center prepared the medication, which was delivered in a blinded manner. Investigators were provided with the trial number of each patient. The result of the randomization was kept in a sealed envelope only to be opened in case of a serious adverse event. Otherwise, after completion of the trial, these envelopes had to be returned sealed.

Patients were enrolled during a 4-month period between March 2001 and July 2001. Investigators and patients remained blinded until week 12, 6 weeks after the placebo-controlled phase had finished. At week 12, investigators and patients were unblinded via a second sealed envelope, so patients who had been in the placebo group could continue treatment with etanercept for an additional 6 weeks, and patients who had started in the etanercept group could stop treatment. After the treatment period, both groups were followed up: the total observational period lasted 30 weeks for patients in the placebo group and 24 weeks for patients in the etanercept group (Figure 1). During the observational period, outcome assessments were performed every 3 weeks.

Study medication. Patients were randomized to receive either placebo or etanercept at a dosage of 25 mg twice weekly by subcutaneous administration during the first 6 weeks of the study. To obtain a 25-mg dose, vials, which contained 10 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine, were used. Three vials were reconstituted with 1 ml of bacteriostatic water. Then the reconstituted drug was

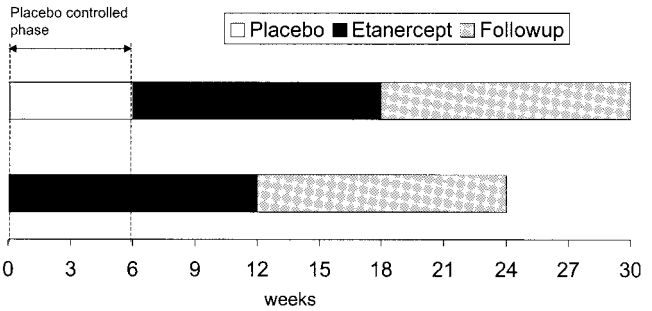

Figure 1. Trial design.

drawn into 2 syringes with equal volumes (1.25 ml each), which were administered at 2 different injection sites. The placebo solution containing bacteriostatic water was supplied and administered identically. After week 6, patients in the placebo group were switched to etanercept for the next 12 weeks, and patients in the etanercept group continued to receive etanercept for another 6 weeks, to ensure that all patients received etanercept for a total of 3 months.

Clinical response. The core set of end points recently proposed by the Assessments in Ankylosing Spondylitis (ASAS) Working Group (22) was used to measure the clinical benefit of etanercept therapy in AS. The following validated questionnaires were filled out by the patients every 3 weeks: the BASDAI (6 questions, relating to fatigue, spinal pain, peripheral arthritis, enthesitis, and morning stiffness assessed both qualitatively and quantitatively on a numeric rating scale) to measure disease activity (21); the Bath AS Functional Index (BASFI) (23) (10 questions about daily life functions) to measure physical function; and numeric rating scales of 0–10 (10 = very bad; 0 = very good) to measure spinal pain and patient and physician global assessment. The Bath AS Metrology Index (BASMI) (24), used to grade mobility of the spine and hips, was administered to each patient by the same rheumatologist.

In addition, the 20% improvement and partial remission criteria recently proposed by the ASAS Working Group (25) were assessed. These criteria define 20% improvement as an improvement of $\geq$20% and an absolute improvement of $\geq$10 units (on a scale of 0–100) in at least 3 of the following 4 domains: patient global assessment, pain, function (represented by the BASFI score), and inflammation (represented by the mean of the 2 morning stiffness–related BASDAI scores). Importantly, deterioration in the potential remaining domain, defined as a change for the worse of $\geq$20% and net worsening of $\geq$10 units (on a scale of 0–100), has to be absent. Partial remission was defined as a value of $<$20 (on a scale of 0–100) in each of the 4 domains. In analogy to RA, we defined a 50% improvement as an improvement of at least 50% and an absolute improvement of at least 20 on a visual analog scale (0–100) in at least 3 of the 4 domains according to the ASAS criteria, together with an absence of deterioration in the remaining domain.

Health-related quality-of-life assessments were performed at baseline and every 6 weeks until week 30, using the Short Form 36 (SF-36) instrument (26). The individual subscales of the survey were grouped into physical- and mental-component summary scores, each of which was assigned on the basis of US population data (26). The scoring algorithm of the Medical Outcome Trust (27) was used to check and calculate the SF-36 as well as for the handling of single missing items in this questionnaire.

As the primary end point of the study, an improvement in disease activity of $\geq$50% between baseline and week 6, measured by the BASDAI, was chosen. The secondary outcome parameters analyzed were improvements in numeric rating scale for spinal pain, BASFI, BASMI, SF-36, the ASAS response criteria, serum C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR).

We also investigated the time to relapse after cessation of the etanercept treatment. The time until relapse occurred was assessed only in patients who had achieved at least a 20% improvement in disease activity (BASDAI) after 3 months of etanercept treatment, compared with baseline. The definition of the time to relapse was the time between the end of the etanercept treatment and the first visit in which an increase of at least 2 in the BASDAI value (range 0–10), compared with the last value at the end of the treatment period, was noted.

Radiographic evaluation. Radiographic assessments of the sacroiliac (SI) joints were routinely performed. Imaging of the spine and other joints was performed only in the presence of appropriate clinical symptoms. The Bath AS Radiology Index for the spine (BASRI-s) (28) was used to grade spine changes. A total score of 2–12 is obtained by adding the scores for the SI joint (0–4, minimally 2 in all patients with AS) to the scores for the lumbar and the cervical spine (each 0–4). BASRI-s values were assessed in 26 of 30 patients (87%). Among the remaining 4 patients, radiographs of the lumbar spine were not obtained in 1 and radiographs of the cervical spine in 3, because the patients were asymptomatic in these areas.

Statistical analysis. Based on recent NSAID trials (29), a placebo response of at least 15% was expected, and based on our previous open-label trial with infliximab in the treatment of AS (15), a response rate of at least 70% was anticipated. A sample size of 15 patients per group was calculated to be sufficient to detect a significant difference with a power of $>$88% at $\alpha = 0.05$ by Fisher's 1-sided exact test. The 1-sided test was used because our primary aim was to detect a higher response rate in the etanercept group compared with placebo. The remainder of the data were all analyzed using 2-sided statistical tests. An intent-to-treat analysis was performed to analyze the response criteria; comparisons were made by Fisher's exact test. Ninety-five percent exact Clopper/Pearson confidence bounds were calculated for the response rates. Dropouts and patients who violated the study protocol were treated as nonresponders.

Means were compared by analysis of covariance with the baseline value as covariable; values at baseline were compared by Wilcoxon's unpaired rank sum test. The paired *t*-test was used for comparing changes within single BASDAI items. *P* values less than 0.05 were considered significant.

Three patients were withdrawn shortly after randomization before receiving the study drug, due to lack of compliance (n = 2) and surgery for a vertebral fracture (n = 1) (all listed as "Did not receive treatment as allocated" in Figure 2). These 3 patients were excluded from further analyses. A fourth

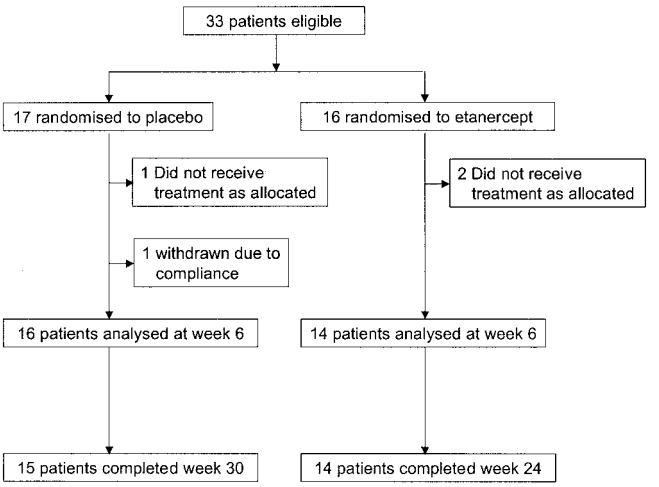

Figure 2. Randomization and followup of patients.

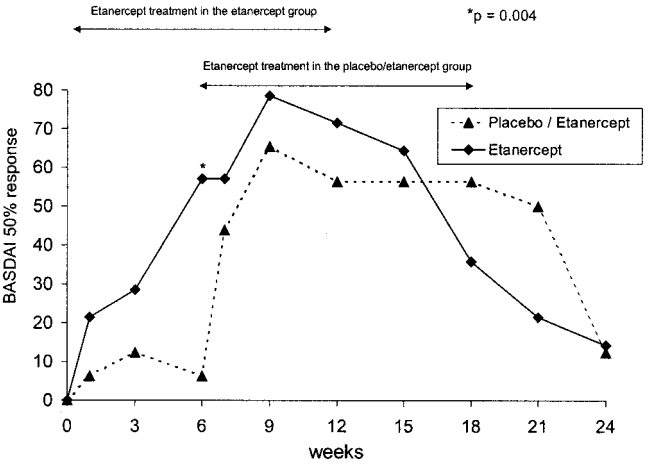

Figure 3. Percent of patients responding to treatment, as indicated by an improvement of ≥50% in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). The *P* value (etanercept group versus placebo group at week 6) was determined by Fisher's exact test.

patient dropped out after 1 week of treatment due to lack of compliance.

RESULTS

Characteristics of the randomized population. At the baseline, the 2 treatment groups showed no significant differences in terms of sex distribution, disease duration, HLA–B27 status, radiographic changes in the spine, and clinical disease parameters, but the patients in the placebo group happened to be somewhat younger (Table 1). All questionnaires including the SF-36 were completed at all time points except for the missing visits of the patient who dropped out, 1 missing visit in a patient who completed the study, and some single missing items in the physical function and mental health SF-36 scales, which were handled according to the manual's instructions (27).

Table 1. Baseline characteristics of the ankylosing spondylitis patients*

Characteristic	Etanercept group (n = 14)	Placebo group (n = 16)
No. male/no. female	10/4	12/4
Age, years	39.8 ± 9.1	32.0 ± 7.5†
Disease duration, years	14.9 ± 8.3	11.4 ± 8.8
No. (%) HLA–B27 positive	12 (85.7)	15 (93.8)
No. of swollen joints (possible range 0–68)	0.9 ± 1.5	1.7 ± 4.0
No. of enthesitic regions (possible range 0–12)	1.4 ± 2.2	1.3 ± 1.7
No. (%) with history of anterior uveitis	5 (35.7)	3 (18.8)
BASDAI	6.5 ± 1.2	6.6 ± 1.0
BASFI	6.2 ± 1.8	5.3 ± 2.3
BASMI	4.1 ± 1.7	3.8 ± 2.1
Pain, numeric rating scale	7.4 ± 1.8	7.6 ± 1.2
Radiologic score (spine), BASRI-s	6.3 ± 2.5	5.4 ± 1.7

* Except where indicated otherwise, values are the mean ± SD. BASDAI = Bath Ankylosing Spondylitis Activity Index; BASFI = Bath AS Functional Index; BASMI = Bath AS Metrology Index; BASRI-s = Bath AS Radiology Index for the spine (obtained in 12 patients in the etanercept group and 14 in the placebo group).
† $P < 0.05$ versus etanercept group, by Wilcoxon's rank sum test.

Efficacy. Etanercept proved efficacious as judged by every response criterion applied. The percentage of patients with a 50% response increased continuously over 6 weeks (Figure 3). The intent-to-treat primary efficacy analysis performed with the data from week 6 showed that 8 patients (57% [95% confidence interval 35–83%]) treated with etanercept and only 1 treated with placebo (6% [95% confidence interval 2–30%]) achieved ≥50% improvement in the BASDAI (P = 0.004). The maximal response (50% improvement in the BASDAI) was obtained most frequently at week 9 in the etanercept group (78%) and at week 3 after switching to etanercept treatment in the group that initially received placebo (62%). After 12 weeks of treatment with etanercept, 71% of patients initially treated with etanercept and 56% of patients who received etanercept after placebo treatment showed a 50% response.

A significantly higher percentage of patients treated with etanercept compared with placebo showed a ≥20% improvement in the BASDAI at week 6 (85.7% versus 31.3%; P = 0.004). Only 1 patient in the etanercept group, and none in the placebo group, achieved ≥70% improvement.

The mean ± SD improvement in the BASDAI increased continuously in the etanercept group, with the score improving from 6.5 ± 1.2 at baseline to 3.5 ± 1.9

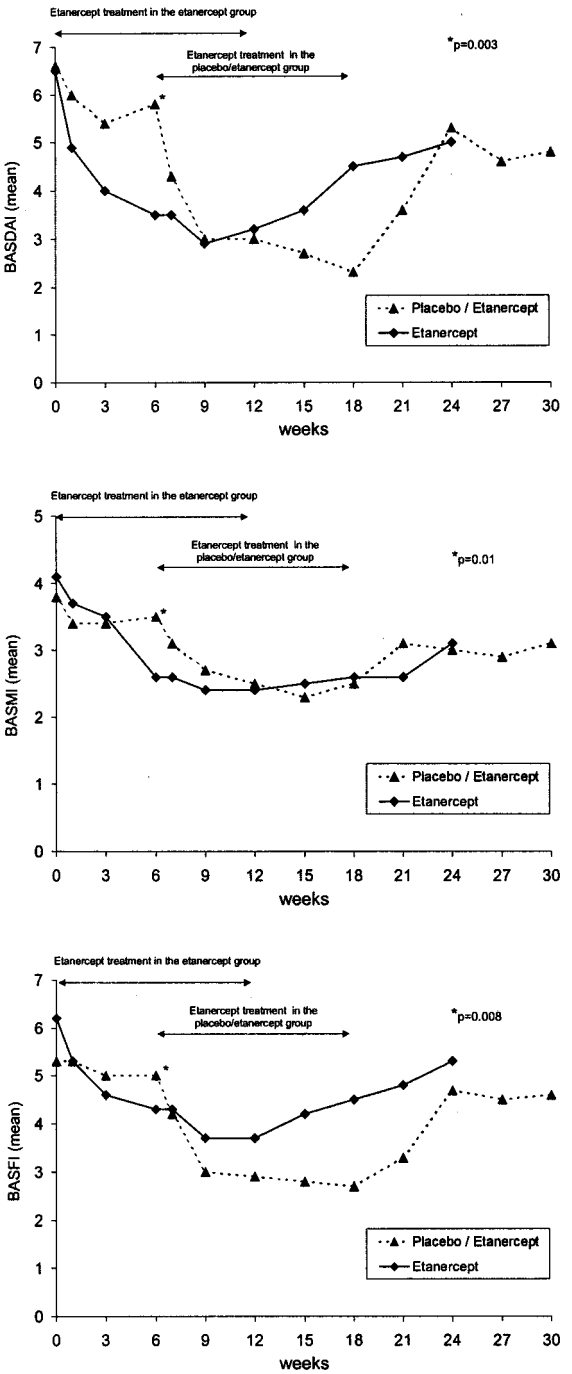

Figure 4. Mean scores on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath AS Metrology Index (BASMI), and Bath AS Functional Index (BASFI) before, during, and after treatment with etanercept or placebo. *P* values (etanercept group versus placebo group at week 6) were determined by analysis of covariance.

at week 6 ($P < 0.0001$), compared with 6.6 ± 1.0 to 5.8 ± 2.0 in the placebo group ($P = 0.003$ for the difference between groups (Figure 4).

All single items in the BASDAI analyzed separately also improved significantly. Specifically, in the etanercept group, mean ± SD values between baseline and week 6 improved from 6.9 ± 1.2 to 4.5 ± 1.7 ($P = 0.0002$) for fatigue, 7.6 ± 1.3 to 3.9 ± 2.1 ($P < 0.0001$) for spinal pain, 5.4 ± 2.8 to 3.1 ± 2.4 ($P = 0.002$) for peripheral joint pain, 7.0 ± 1.7 to 3.6 ± 2.4 ($P < 0.0001$) for entheseal pain, and 5.5 ± 2.1 to 2.5 ± 1.5 ($P = 0.0003$) for morning stiffness. No significant changes were observed in the placebo group.

The superior improvement in the etanercept group compared with the placebo group at week 6 could also be substantiated by applying the ASAS Working Group criteria for 20% improvement (78.6% versus 25% of the patients in the etanercept group and the placebo group, respectively) and 50% improvement (42.9% versus 12.5%, respectively) (both $P < 0.01$). No patient was judged to be in partial remission at week 6 since none had a pain score of <2 at that time point. Ten of 30 patients (33.3%) were in partial remission after 12 weeks of treatment with etanercept.

The same differences and trends that were observed with the BASDAI scores were found when the BASFI and BASMI scores were analyzed (Figure 4). Between baseline and week 6, the mean ± SD BASFI score improved significantly in the etanercept group (from 6.2 ± 1.8 to 4.3 ± 2.3) but not in the placebo group (5.3 ± 2.3 to 5.1 ± 2.4) ($P = 0.008$ between groups). BASMI scores showed similar improvement in the etanercept-treated group between baseline and week 6 (4.1 to 2.6), whereas no significant change was observed in the placebo group (3.8 ± 2.1 to 3.5 ± 2.3) ($P = 0.01$ between groups).

In patients with peripheral arthritis and enthesitis, signs and symptoms improved somewhat after 6 weeks of etanercept therapy. Five patients (35.7%) in the etanercept group had peripheral arthritis and 5 (35.7%) had enthesitis at baseline. At week 6, 3 patients still had peripheral arthritis and 4 had enthesitis. No change was seen in the placebo group ($P > 0.05$ for arthritis and enthesitis, etanercept group versus placebo group at week 6).

A significant number of etanercept-treated patients either stopped NSAID use (38%) or reduced their NSAID dosage by 50% (62%) between baseline and week 6. In comparison, fewer placebo-treated patients were able to reduce their NSAID dosage by 50% (7%; $P = 0.016$ versus etanercept group) or to stop NSAIDs (13%; $P = 0.069$ versus etanercept group). Compared with baseline, the mean ± SD CRP levels decreased from 19 ± 17 mg/liter to normal (<6 ± 4 mg/liter) at week 6 ($P = 0.001$ versus placebo group). ESR levels

also decreased significantly in the etanercept group ($P = 0.01$ versus placebo group). Between baseline and week 6, the physical component score assessed with the SF-36 improved in the etanercept group but not in the placebo group. The difference between the scores in the 2 groups at week 6 reached statistical significance ($P = 0.026$). No improvement was seen in the mental component score in either group during the first 6 weeks.

Five patients in the etanercept group and 3 in the placebo group had a history of acute anterior uveitis. Between baseline and week 6, no patient in either treatment group had a new episode of anterior uveitis. During the entire 12-week period of treatment with etanercept, only 1 patient (who had started in the placebo group) had a new episode of anterior uveitis.

After week 6, when the patients initially treated with placebo were switched to a 12-week regimen of etanercept, they exhibited a response in all outcome measures that was similar to the response observed in the group that had begun the study in the etanercept group. Response in both groups was sustained or increased throughout the 12 weeks of treatment with etanercept (Figures 3 and 4).

Followup. Twenty-four of the 30 patients had at least 20% improvement in the BASDAI, and the time to relapse after cessation of treatment was estimated in these patients. After cessation of treatment with etanercept, 18 of the 24 patients (75%) experienced a relapse (as defined in Patients and Methods) within the followup period of 3 months. The mean ± SD time to relapse was 6.2 ± 3.0 weeks. The remaining 6 patients (25%) relapsed later. All patients who had a relapse were included in a 1-year open extension of the trial; these data will be reported at a later time.

Adverse events. There were no serious adverse events or withdrawals because of adverse events, and the 2 groups did not differ significantly with regard to either the overall rate of adverse events or the rates of specific events in weeks 0–6. The most common adverse events were reactions at the injection site and minor infections. Two patients in the etanercept group and none in the placebo group had an injection-site reaction. Minor uncomplicated infections of the upper respiratory tract occurred in 6 patients each in the etanercept group and the placebo group. All other adverse events occurred only in single patients in both treatment groups and were classified as mild to moderate.

DISCUSSION

The findings of this investigator-driven randomized controlled trial not only confirm the clear-cut efficacy of etanercept in the treatment of patients with active AS who are receiving conventional NSAID therapy (29) but, in comparison with the recently published results of a trial in California (19), also show that no additional therapy with DMARDs and steroids is needed to obtain this result. This is important because many patients with active AS are treated with DMARDs and glucocorticoids (8,30) despite lack of proven efficacy and approval, simply because no other medical therapy had been available (31). There is very limited evidence for a treatment effect of sulfasalazine on spinal involvement in AS (32), while there is some evidence for its efficacy in patients with peripheral arthritis (33). Other than the findings in some uncontrolled open and retrospective studies (some yielding positive and some negative results), there is no evidence of efficacy of methotrexate for either peripheral or axial involvement in AS (34–36). As in our previous studies (17), we focused on axial involvement in this study: only 36% of the patients had peripheral joint manifestations.

This study had a relatively short placebo-controlled period. A 6-week period of placebo treatment is unusual in DMARD studies but has been shown to be sufficient for NSAID trials (37). It should be stressed, however, that there is a major difference between trials evaluating NSAID efficacy and those evaluating anti-TNFα efficacy: in the former, the flare design is used (i.e., patients do not receive the study drug or placebo until they have a flare), while in the latter, patients who have active disease despite NSAIDs are treated. This needs to be kept in mind when comparing responses based on the ASAS Working Group 20% improvement criteria. Only 50% of the AS patients evaluated in NSAID trials reach 20% improvement (25). This indicates that many AS patients are insufficiently treated with NSAIDs. Although anti-TNFα therapy has not been classified as a symptom-modifying antirheumatic drug (SMARD) or a disease-controlling antirheumatic drug (DCARD) or even a steroid-like drug, the results of this short-term trial at least indicate strong modification of disease-associated signs and symptoms. Anti-TNFα therapy probably could be regarded as both an SMARD and a DCARD because of its ability to affect signs and symptoms on a short-term and a long-term basis. Our results demonstrated that function, spinal mobility, and quality of life were positively influenced by etanercept therapy, which may be taken as evidence that the overall efficacy of anti-TNFα therapy in AS is so strong that clinically relevant differences can be shown even after 6 weeks. The decision to choose this rather short period for the placebo-controlled portion of the

study was based mainly on the relative shortage of study medication that was initially available.

In contrast to the previously published trial by Gorman and colleagues (19), we used validated outcome instruments such as the BASDAI (21) and the BASMI (24), as proposed by the ASAS Working Group (22). This facilitates comparison with data obtained in our infliximab trial (17) and to be obtained in future studies. It is our impression that the 2 drugs work equally well in our patients. This can be substantiated by the percentages of patients with improvement in these studies (50% response on the BASDAI seen in 53% of patients in the infliximab trial [17] and 57% in this etanercept trial). The clinical impression that the onset of improvement may be faster with infliximab cannot be substantiated by the data from this study, because we did not perform the adequate measurements at week 1 in the infliximab trial. With etanercept there was improvement already at week 1 but this was not significant, probably due to the limited number of patients. At week 6, our results were more consistent than those in the California study (19), which included a larger number of patients; in that study, the difference between placebo and etanercept was not significant at this time point. However, at all time points after week 6, the efficacy of etanercept was clear and significant in both studies, and after patients initially in the placebo group were switched to etanercept, the strong efficacy was confirmed, as also found through week 40 in the other controlled study of etanercept in AS (19) and through week 24 in an open study in SpA (18).

The time at which the highest percentage of patients in the etanercept group showed a response was week 9, when almost 80% of the patients had a response as indicated by a $\geq$50% improvement in the BASDAI. In the placebo group, the maximum percentage showed a response at an earlier time point after the switch to etanercept. After 12 weeks of etanercept therapy, 33% of the patients treated were in partial remission according to the ASAS criteria, marginally better than in the infliximab trial. However, the small numbers do not allow for definite comparisons with infliximab. More importantly, both anti-TNFα agents were found to be substantially superior to NSAIDs.

Several groups have reported that, irrespective of clinical symptoms, as many as 60% of AS patients have microscopic and macroscopic evidence of gut inflammation similar to Crohn's disease (38). Since etanercept has no efficacy in Crohn's disease and, in fact, flares of Crohn's disease during etanercept treatment have been observed (39), there is no reason to think the efficacy of anti-TNFα therapy is related to a positive treatment effect on gut lesions. In contrast, our results indicate that spinal inflammation can be improved despite ongoing gut inflammation, suggesting that gut inflammation has no major role in the pathogenesis of spondylitis in AS. Indeed, peripheral arthritis in SpA seems to have a much stronger link to gut inflammation than does spine disease (40). Although our study did not include enough patients with peripheral arthritis and enthesitis to demonstrate that etanercept is also beneficial for these disease manifestations, there is no reason to believe it is not. In our own and others' clinical experience and in randomized controlled trials performed with psoriatic arthritis patients (41), etanercept is clearly efficacious for these disease manifestations, and this has also been reported in published trials that included patients with AS (18,19).

In contrast to the infliximab trial (17), we were not able to determine treatment responses in patient subgroups in this study since the numbers were small. In particular, the percentages of patients with low CRP levels and of HLA–B27–negative patients were too low to enable statistical analysis.

Our careful recording of the patients' courses after cessation of therapy provided further important information. Uniform criteria to identify relapse had to be applied. On the basis of our experience and preliminary data on the smallest detectable difference and the minimal clinically important difference in the BASDAI (Dougados M: personal communication), we choose a deterioration of $\geq$2 points in the BASDAI to be taken as evidence of relapse. This cutoff clearly needs to be further validated. However, in our study it proved quite useful since we observed that 75% of the patients relapsed after a mean of 6 weeks. The remainder of the patients relapsed some weeks later, but all ultimately did relapse.

Although anti-TNFα therapy seems to be generally well tolerated, severe side effects of both etanercept and infliximab have occurred in some rare cases (42–45). The actual status of reported adverse events can be obtained from the FDA Web site at www.fda.gov. Although severe side effects seem to be rare, patients treated with anti-TNFα must be monitored closely. In this study no major adverse events were observed. This is in contrast to our larger study with infliximab, in which 1 case of tuberculosis occurred (17).

In conclusion, etanercept was proven efficacious in the treatment of active AS. In the absence of reasonable alternatives, we expect that 20–30% of patients with AS are candidates for treatment with biologic agents.

This is the percentage of patients in databases whose disease is regarded as severe and active (8). If spinal inflammation is constantly suppressed, as can be assumed according to the results of reported MRI studies (46), there is clearly hope that new bone formation and ankylosis can be prevented by anti-TNFα therapy. This needs to be substantiated in future studies. Even if this is not the case, it can be expected that anti-TNFα treatment will be meaningful on a socioeconomic basis since patients with AS are young and often gainfully employed, and the disease may affect their employment situation. Many socioeconomic effects of AS, such as days of sick leave, unemployment and early retirement, and other indirect and direct costs, have been addressed in recent trials (8,9). It seems likely that anti-TNFα therapy can positively affect some of these factors (47).

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