Sustained efficacy and safety, including patient-reported outcomes, with etanercept treatment over 5 years in patients with ankylosing spondylitis

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Abstract

Objectives

To assess long-term safety and clinical efficacy of etanercept 25 mg subcutaneously twice weekly up to 5 years in subjects with ankylosing spondylitis (AS).

Methods

An open-label (OL), multicentre, phase 4, 156-week extension study of subjects with AS who had completed a 12-week randomised, placebo-controlled study (N=84; n=45 etanercept, n=39 placebo) followed by a 96-week OL study (n=81; n=42 etanercept/etanercept; n=39 placebo/etanercept); 59 subjects who completed the 96-week OL extension enrolled in the current OL trial and continued etanercept 25 mg BIW for an additional 156 weeks (total duration: 264 weeks, original etanercept group; 252 weeks, original placebo group). Safety was based on spontaneous reports of adverse events (AEs). Last observation carried forward was used for imputation of missing values.

Results

Thirty-seven of 59 subjects (63%) completed 5 years of etanercept treatment. Serious non infectious AEs and serious infections occurred at a rate of 0.17 and 0.03 events per subject years, respectively; inflammatory bowel disease and uveitis (including iritis and iridiocyclitis) occurred at 0.01 and 0.14, respectively. No cases of tuberculosis or opportunistic infections were reported. Assessment in Ankylosing Spondylitis (ASAS) responses and improvements in Bath Ankylosing Spondylitis Functional Index and spinal mobility were sustained from week 108 through week 264.

Conclusion

Etanercept was well tolerated with no new safety signals detected in subjects with AS over 5 years. Clinical efficacy and improvements in function and mobility seen during the double-blind and first OL study were sustained. These results support etanercept therapy for the long-term management of this chronic disease.

Key words

Etanercept, spondyloarthritis, anti-TNF, physical function.

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Introduction

Ankylosing spondylitis (AS) is a chronic spondyloarthropathy that primarily affects the spine, producing pain and stiffness due to inflammation of the sacroiliac, intervertebral, and costovertebral joints, occurring predominantly in young men (1). Over time, there can be a major reduction in spinal mobility resulting in a progressive loss of physical function (1).

Tumour necrosis factor (TNF) plays a major role in the pathogenesis of AS. TNF levels are elevated in the serum (2, 3) and synovial tissue (4-6) of subjects with AS. Treatment with etanercept, a fully human TNF-α soluble receptor, reduces disease activity, pain, and stiffness (7-12) in subjects with AS, improving mobility and quality of life (13, 14). In randomised clinical trials in subjects with AS (7-9, 15), etanercept effectively reduced disease activity and rapidly improved functioning and spinal mobility as measured by multiple variables. The trials demonstrated that this agent was well tolerated for up to 24 weeks of therapy (9, 15).

To establish the long-term safety and sustained efficacy of etanercept in subjects with AS, open-label extensions (16, 17) of the major phase 3 trials of etanercept (9, 15) were carried out. In the open-label extension of the Davis *et al*. double-blind study (17), etanercept was well tolerated and efficacy, including function and spinal mobility, persisted throughout the 4-year duration of the trial. The Calin *et al*. double-blind study (9) was followed by 2 open-label extensions for a total of up to 5 years of etanercept exposure. In the first open-label extension (16), etanercept continued to be well tolerated and the efficacy, including physical function and spinal mobility improvements achieved early during etanercept therapy, was sustained through the 2 years of the study (16). Subjects who completed the first open-label extension (16) were eligible to enter the second, 3-year extension. The results from the second open-label extension are reported here.

Patients and methods

Study design

An open-label, multicentre, phase 4, 156-week (3-year) extension study evaluated long-term safety and efficacy of etanercept in subjects with AS who completed a 12-week (3-month) randomised, placebo-controlled study (9) followed by a 96-week (2-year) open-label study (16) (Fig. 1). During the second extension, safety and efficacy, including mobility assessments, were made at baseline and at ~3-month intervals. Spontaneous reports of adverse events (AEs) were collected throughout the trial.

The study was conducted from April 2004 to July 2007 in 14 centres in 8 European countries in accordance with the ethical principles of the Declaration of Helsinki and was consistent with the guidelines for Good Clinical Practice. The study protocol and informed consent form were approved by each institution's review board or independent ethics committee.

Subjects

Adult subjects (aged ≥18 years) who had previously completed a 3-month randomised, placebo-controlled study (9) followed by a 2-year open-label study (16) were eligible to participate. Enrolment criteria were the same as those described for the double-blind study (9).

Treatment

All subjects received etanercept 25 mg subcutaneously twice weekly for 3 additional years (156 weeks).

Safety assessments

Assessments were based on reports of AEs, results of routine physical examinations, and laboratory determinations from this 3-year extension study. The National Cancer Institute (NCI) grading scale was used to identify subjects with abnormal laboratory test results for hematology and biochemistry. NCI grades 3 and 4 were considered to be of potential clinical importance. AEs that coded to the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) preferred term uveitis or iritis (iridiocyclitis, a verbatim term, codes to uveitis) were recorded as uveitis events for simplicity; AEs that coded to the preferred term of colitis,

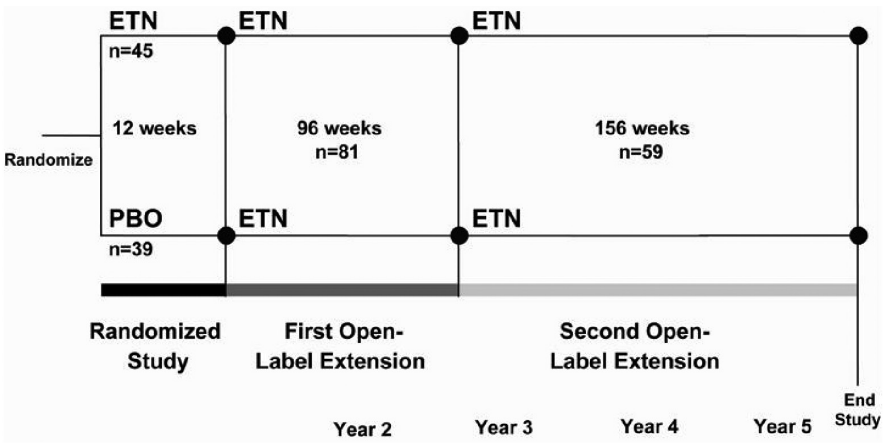

Fig. 1. Study design.

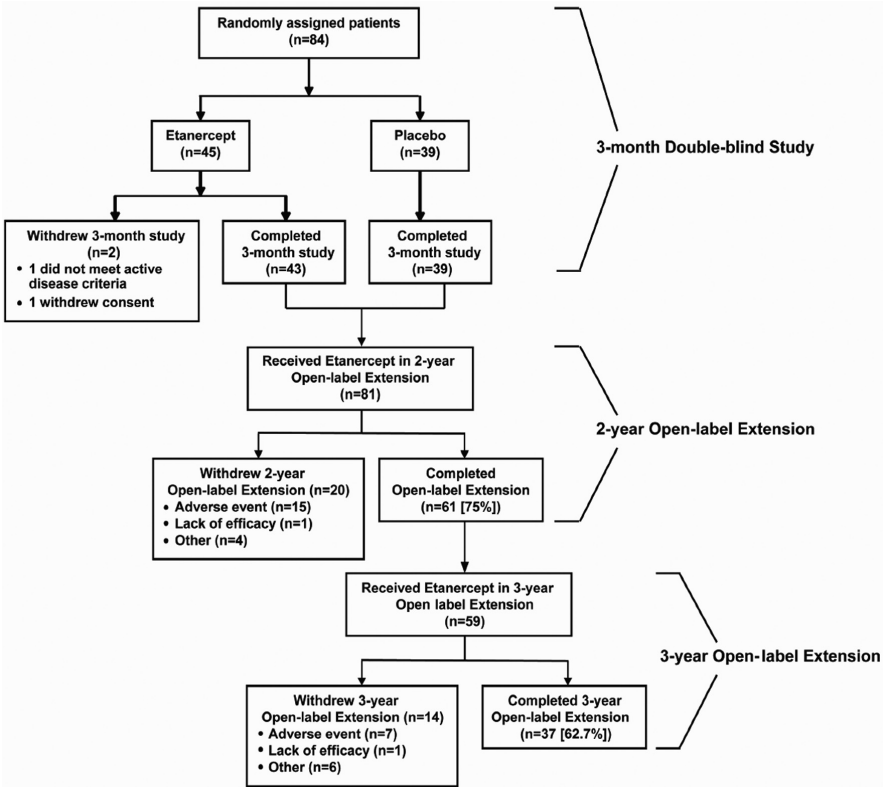

Fig. 2. Subject disposition.

colitis ulcer, ileitis and proctitis ulcer, or Crohn's disease were recorded as inflammatory bowel disease (IBD).

Efficacy assessments

Improvement in AS, as defined by the Assessment in Ankylosing Spondylitis (ASAS) criteria (18) was a key measure; the individual core components of the ASAS criteria, including Bath Ankylosing Spondylitis Functional Index (BASFI), subject global assessment of disease activity, back pain (total and nocturnal), and morning stiffness, were also assessed. Other variables assessed were Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), physician global assessments of disease, spinal mobility as measured by the modified Schober's test, chest expansion scores, and occiput-to-wall distance, number of painful and swollen joints, C-reactive protein (CRP) levels, and percentage of subjects achieving partial remission (defined as a score below 20 in each of the four ASAS domains: subject global assessment, pain, function, and inflammation) (18).

BASDAI 50 was performed as a post hoc efficacy analysis because it was recommended as a monitoring assessment tool in the International Consensus Statement for use of anti-TNF agents in subjects with AS. BASDAI 50 is defined as a 50% or greater relative change or an absolute change of at least 2 (scale of 0–10) in the BASDAI. ASAS 40 and ASAS 5/6 (18) were also performed as post-hoc analyses.

Statistical analyses

Because this was an open-label study, the efficacy and safety analyses are descriptive. The last-observation-carried-forward (LOCF) method was used for imputing missing values. All randomised subjects who received at least 1 dose of test article were included in the safety and efficacy analyses.

Results

Subjects and characteristics

Of 84 subjects with active AS enrolled in the 3-month, randomised, double-blind, placebo-controlled trial (etanercept 25mg subcutaneously twice weekly) (9), 81 continued into the first open-label treatment and 61 completed it (16). Fifty-nine subjects (n=32, original etanercept; n=27, original placebo) who completed the first 2-year open-label extension were enrolled in the second extension and continued to receive open-label etanercept for an additional 3 years (Fig. 2). Over the 5 years, total etanercept exposure accrued was 287.01 subject years; etanercept exposure accrued during the second extension was 145.64.

The 59 subjects who participated in the second open-label extension were predominantly men (76%), with a mean age of 44 years, and mean disease duration of 14 years (Table I). All 59 subjects received at least 1 dose of etanercept; 37 (62.7%) completed the 3 years of the study (Fig. 2). A total of 14 (23.7%) subjects were discontinued from the study, 7 (11.9%) because of adverse events, 1 (1.7%) for lack of efficacy, and 6 (10.2%) for other reasons including protocol violations and non-medical reasons.

Table I. Demographics and other baseline characteristics (n=59).

Characteristic	Baseline original randomised study Week 0 (n=59)	Baseline current open-label extension study Week 108 (n=59)
Age, mean years	42.1	44.2
Duration of disease, mean years	12.0	14.1
Sex, n (%)		
Female	14 (23.7)	14 (23.7)
Male	45 (76.3)	45 (76.3)
Ethnic origin, n (%)		
White	57 (96.6)	57 (96.6)
Asian	1 (1.7)	1 (1.7)
Other	1 (1.7)	1 (1.7)
BASFI, VAS, mm	56.8	28.5
BASDAI, VAS, mm	59.8	21.8
Total back pain, VAS, mm	58.2	19.8
Morning stiffness, VAS, mm	66.1	22.1
Subject global assessment, VAS, mm	64.7	19.8
Number of painful joints	7.6	1.4
Number of swollen joints	5.1	0.7
C-reactive protein, mg/L	25.3	5.4

Table II. Treatment-emergent adverse events (≥10%).

Treatment-emergent adverse events	Subjects, n (%)
Noninfectious adverse events	
Any adverse event excluding injection site reactions	52 (88.1)
Accidental injury	12 (20.3)
Arthralgia	11 (18.6)
Hypertension	11 (18.6)
Arthritis	10 (16.9)
Uveitis	10 (16.9)
Diarrhea	9 (15.3)
Injection site reaction	7 (11.9)
Abdominal pain	6 (10.2)
Infectious adverse events	
Any infectious event	37 (62.7)
Upper respiratory tract infection	16 (27.1)
Flu syndrome	16 (27.1)
Vaginitis*	2 (14.3)

*Calculation based on number of females only (n=14).

Over the course of the study, 48 (81.4%) subjects were more than 80% compliant with etanercept usage (as assessed by the number of returned used vials). Of the remaining 11 subjects, 3 (5.1%) were less than 80% compliant during the last year and 8 (13.6%) discontinued the study early.

Safety and tolerability

Safety data for the double-blind study and the first 2-year open-label extension study have been published previously (9, 16). Over the 3 years of the second open-label extension, 7 (11.9%) subjects were withdrawn because of AEs (Fig. 2). No AE predominantly led to discontinuation; no new safety signals were reported.

During this 3-year extension study, 1 or more treatment-emergent adverse events (excluding infections and injection site reactions) were reported by 52 (88.1%) subjects (Table II). The most frequent treatment-emergent adverse events (excluding infections) were injection site reactions, accidental injury, arthralgia, hypertension, and arthritis; and the most common infections were flu syndrome and upper respiratory tract infection.

During the 3 years of this study, serious adverse events (SAEs) occurred at a rate of 0.21 events per subject year; serious infection occurred at 0.03 events per subject year and serious non-infectious AEs at a rate of 0.17 per subject year. One subject reported both infectious and non-infectious SAEs. Two SAEs were reported by more than 1 subject – myocardial infarction and cholelithiasis (2 subjects each). The 2 subjects who had a myocardial infarction had a history of cardiac disorders and subsequently died. One subject had discontinued etanercept therapy more than 5 months (165 days) prior to the myocardial infarction, which was the cause of death. The other subject discontinued etanercept when he was hospitalised for general malaise. He subsequently had a myocardial infarction, and died as a result of multi-organ failure approximately 1 month after the initial hospitalisation.

Three subjects reported 4 serious infectious events; 1 subject had an acute infection of the sigmoid colon, 1 subject had bilateral pneumonia and progressive sepsis, and 1 subject became HIV seropositive. Etanercept was temporarily discontinued in the subject with acute infection of the sigmoid colon; the subject with bilateral pneumonia and progressive sepsis was discontinued from the study. The third subject, although aware that he was HIV seropositive on day 87, did not inform the investigator until day 380 when he declined further treatment and discontinued from the study. No cases of opportunistic infections, tuberculosis, central demyelinating disease, blood dyscrasias, lupus, discoid lupus erythematosus, or antiphospholipid syndrome were reported.

Three malignancies – metastatic prostate cancer, squamous cell carcinoma of the skin, and chronic lymphoid leukemia stage B – were diagnosed in 3 subjects during the study. In all 3 cases, the investigator considered the event to be probably related to treatment with study drug, and all 3 subjects were discontinued from the study.

No flares of IBD were reported in the 3 subjects with a prior history of IBD Two subjects with no prior history of IBD reported an event of Crohn's disease resulting in a rate of 0.01 events per subject year. Both events were

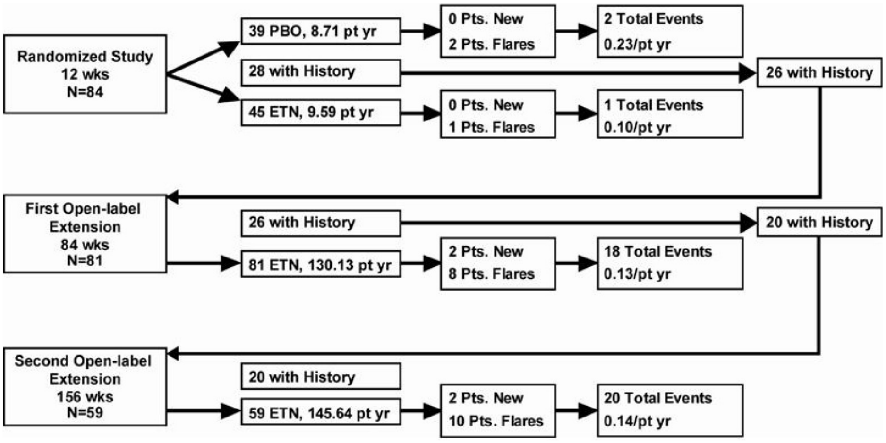

Fig. 3. Uveitis events.

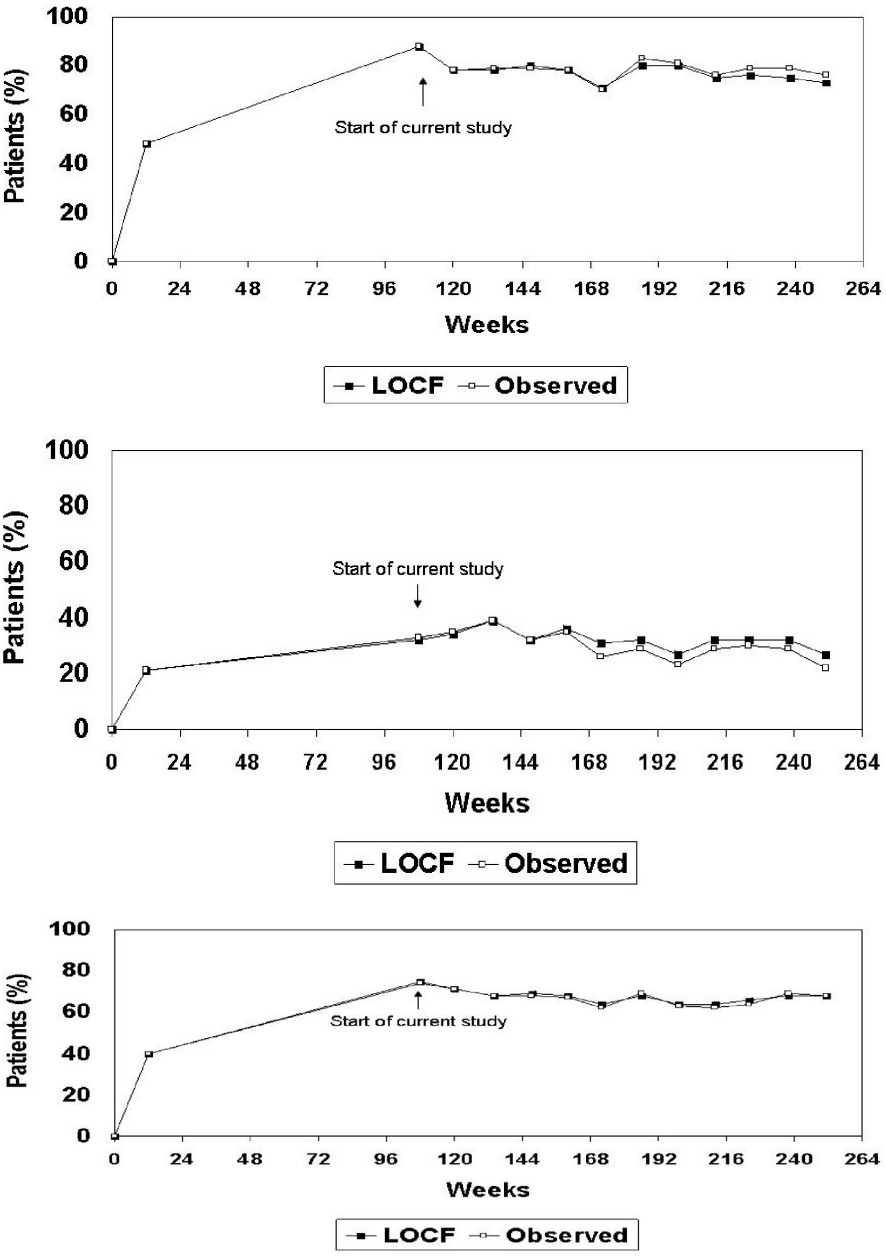

Fig. 4. ASAS 20, ASAS 5/6, and ASAS 40 response rates over time.

considered as probably not related to etanercept by the investigator. Subjects received standard-of-care treatment for the event and were discontinued from the study.

Ten of 20 subjects with a history of uveitis had at least 1 flare during this second open-label extension study (Fig. 3). Eight of the 10 subjects with flares had a history of uveitis before enrollment in the original double-blind study, and 2 had a first event during the first (96-week) open-label extension (16). Two subjects with no prior history had a uveitis event; overall event rate was 0.14 per subject year. The events were generally mild to moderate in severity and resolved with standard-of-care treatment. No withdrawals were related to uveitis but 1 subject, while being treated for uveitis, experienced a severe myocardial infarction and subsequent complications that resulted in death.

Eight NCI grade 3 laboratory test results (6 increased serum bilirubin [range 34-52 μmol/mL; normal 0-22 μmol/mL], 1 decreased lymphocyte count [0.28 x 10^9/L; normal ≥1.5 x 10^9/L], and 1 decreased neutrophil count [0.88 x 10^9/L; normal ≥2.0 x 10^9/L]) reported in 4 subjects were not associated with any clinical AEs leading to discontinuation. No grade 4 laboratory test results were reported during the study.

Clinical efficacy

– Disease activity assessments

In this second open-label extension study, the ASAS 20, ASAS 40, and ASAS 5/6 responses to etanercept treatment were sustained over time (Fig. 4). The proportions of subjects classified as responders in each ASAS response category did not change appreciably through the final week (week 156 of this second extension study). The percentage of ASAS 20 responders was 88% at 2 years (baseline of the current second open-label study) and 75% after 5 years of etanercept therapy. ASAS 40 was achieved by 68% (n=40) of subjects, and ASAS5/6 was achieved by 32% (n=19) of subjects after 5 years (Fig. 4).

The mean BASDAI score at 2 years (baseline of this study) was 21.8 mm; a 63.6% improvement from the original double-blind study baseline. After

5 years, the mean BASDAI score was 26.6 mm, a 55.5% improvement from the original baseline value (Fig. 5A). BASDAI 50 was also sustained during this period (Table III).

– Physical function and mobility

During the original double-blind study, mean BASFI scores for the group receiving etanercept were significantly lower than for the group receiving placebo after just 1 month of therapy ($p<0.05$) (9). Improvement in BASFI from the original baseline was also sustained through the study (Fig. 5B).

Spinal mobility, as assessed by the Modified Schober's test, chest expansion, and occiput-to-wall measurements, was sustained through the 3-year duration of this study (Fig. 5C and Table III). Improvements in morning stiffness and total back pain were sustained over this period as well (Table III).

– Peripheral arthritis

The mean painful joint count at 2 years was 1.4, or an 82.2% improvement from the original (double-blind study) baseline value of 7.6 (before any treatment). At year 5, the mean painful joint count was 0.9 or a mean percentage improvement of 88.7% (Table III).

The mean swollen joint count at baseline of the current study was 0.7, which was an 85.4% improvement from the original study baseline value of 5.1. At 5 years, the mean swollen joint count was 0.7, or a mean percentage improvement of 85.4% (Table III).

– Partial remission

Partial remission was sustained through the 3-year duration of the second open-label study (Table IV). The percentage of subjects who achieved partial remission at study baseline and 5 years was 37% and 31%, respectively.

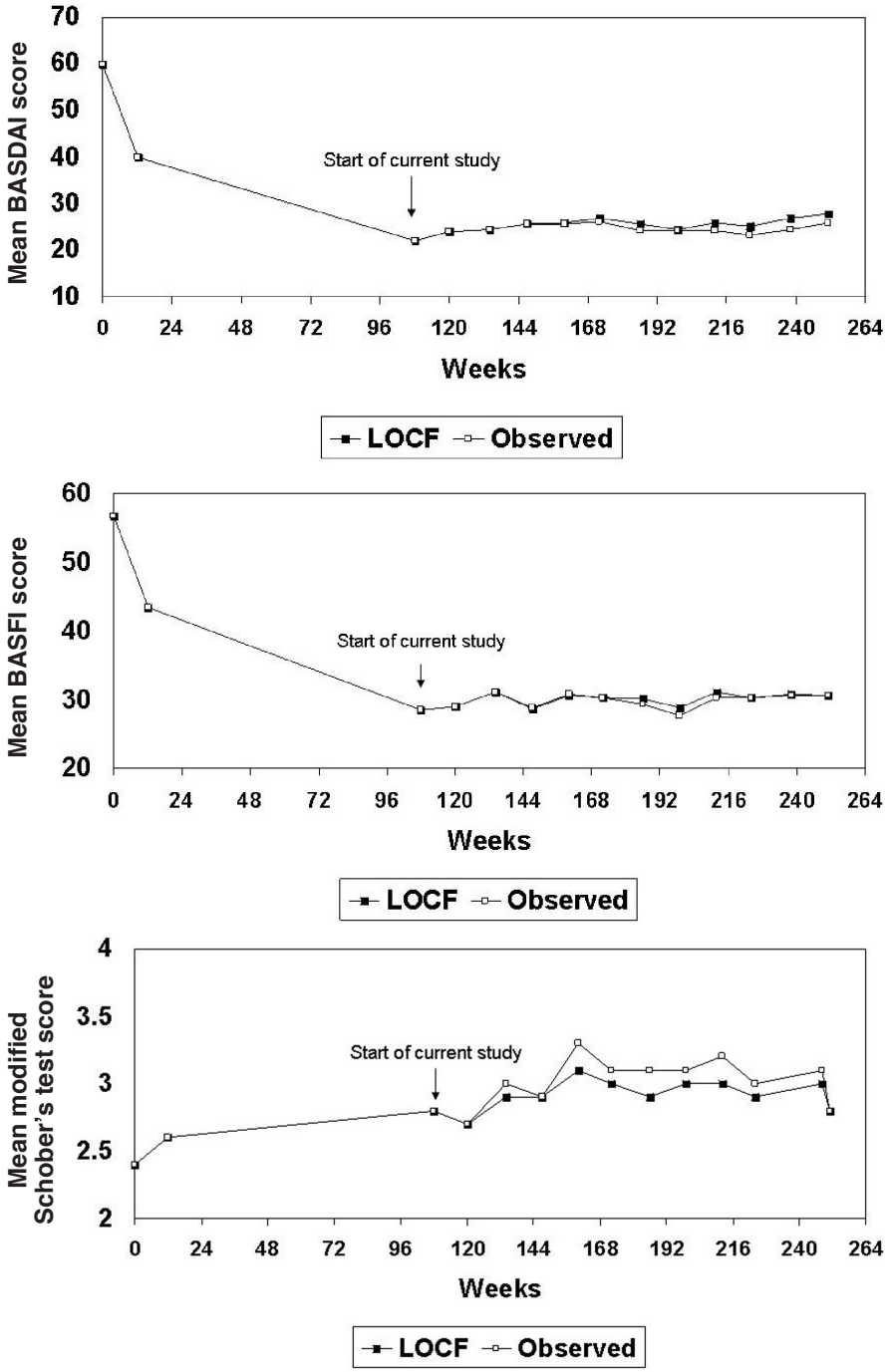

Fig. 5. Mean BASDAI, mean BASFI, and mean Modified Schober's test over time.

Discussion

This 3-year study is the second extension study of a 3-month placebo-controlled, double-blind study (9) that evaluated the safety and efficacy of etanercept in subjects with AS. Etanercept continued to be well tolerated, and there were no unexpected safety findings. The rates of noninfectious AEs, infections, and injection site reactions per subject year were 2.17, 0.755, and 0.323, respectively. Except for myocardial infarction and cholelithiasis, which occurred in 2 subjects, no other SAEs (infectious or non infectious) occurred more than once. There were no reports of tuberculosis or opportunistic infections.

Subjects with AS are at an increased risk for other inflammatory diseases, such as IBD and uveitis (19). Although there were a few new AE reports related to these extra-articular aspects of AS, the majority of subjects with prior histories of IBD or uveitis did not develop recurrent symptoms of these conditions. There were 2 cases of newly diagnosed IBD in this study, and the 3 subjects with a history of IBD had no relapses. The exposure-adjusted rate of new IBD events was 0.14 per subject year. In a similar long-term study in subjects

Table III. Summary of other efficacy parameters (LOCF).

Efficacy parameter (Percentage improvement from Week 0)	Original study baseline (Week 0)	Baseline second open-label extension (Week 108)	Week 156 second open-label extension (Week 264)
	Mean n=59	Mean (Mean percentage improvement from original study baseline) (n=59)	
BASDAI score	59.8	21.8 (63.6)	26.6 (55.5)
BASDAI 50, n. (% of subjects)		42 (71)	39 (66)
Individual components of ASAS response criteria			
Subject global assessment of disease activity	64.7	19.8 (69.5)	27.5 (57.5)
Total back pain	58.2	19.6 (66.3)	26.2 (55.0)
Nocturnal back pain	57.2	15.3 (73.2)	24.7 (56.8)
Morning stiffness	66.1	22.1 (66.6)	26.8 (59.4)
BASFI	56.8	28.5 (49.9)	31.5 (44.6)
Other measures of spinal mobility			
Modified Schober's test, cm	2.4	2.8 (16.0)	2.9 (18.9)
Chest expansion, cm	3.7	4.7 (26.1)	4.9 (32.7)
Occiput-to-wall, cm	5.7	4.3 (24.5)	4.2 (26.6)
Joint counts			
Number of swollen joints	5.1	0.7 (85.4)	0.7 (85.4)
Number of painful joints	7.6	1.4 (82.2)	0.9 (88.7)
Acute phase reactants			
C-reactive protein, mg/L	25.3	5.4 (78.8)	9.1 (64.1)

ASAS: Assessment of Ankylosing Spondylitis; BASDAI: Bath Ankylosing Spondylitis Daily Activities Index; BASFI: Bath Ankylosing Spondylitis Functional Index.

Table IV. Number (%) of subjects who achieved partial remission (n=59).

	Treatment Week	n (%)
Randomised	Week 12	9 (16)
Previous 96-week open-label extension	Week 108	22 (37)
Current open-label extension	Week 120	21 (36)
	Week 134	18 (31)
	Week 147	20 (34)
	Week 160	18 (31)
	Week 172	18 (31)
	Week 186	19 (32)
	Week 199	20 (34)
	Week 212	19 (32)
	Week 224	21 (36)
	Week 238	16 (27)
	Week 251	19 (32)
	Week 264	18 (31)

with AS (17), 1 new case of IBD was reported for an exposure-adjusted rate of 0.019 per subject year, and no flares occurred in the 13 subjects who had a history of IBD during the study. A pooled analysis of 9 studies, 7 placebo-controlled an 2 open-label (20), found that the rate of IBD events in subjects receiving etanercept was not different from patients receiving placebo; rates of IBD with the anti-TNF antibodies, infliximab and adalimumab, were lower than the rate with etanercept. The latter observation is not unexpected given the different efficacies of the agents in the treatment of active IBD.

Episodes of uveitis that occurred during the study were generally mild to moderate in severity and resolved following treatment with topical agents; none of the events resulted in discontinuation of the subject from the study. During the 3 years, 2 new events of uveitis were reported and 10 of the 20 subjects with a history of uveitis had at least 1 flare event. Exposure-adjusted rates for the new and flare events were 0.01 and 0.12, respectively. These rates were similar to those reported in the Davis *et al*. (2008) 4-year extension study of etanercept (17). In that study, the exposure-adjusted rates of new and flare events were 0.02 and 0.11, respectively.

The substantial improvements in key clinical end points, such as ASAS 20 and BASDAI, seen after the double-blind study and sustained during the first 2-year extension study (16), persisted during this 3-year study. Improvements from baseline in physical function and spinal mobility were likewise maintained. A total of 31% of the subjects achieved partial remission. Only 1 subject discontinued treatment for lack of efficacy.

Loss of physical function and spinal mobility, are major concerns and may be major reasons for work disability and missed workdays of subjects with AS (21, 22). In the pivotal trials, etanercept resulted in rapid improvement of physical function and mobility (9, 13, 15), which was sustained through 5 years in a 2-year (16) and this 3-year extension. After 5 years, functional impairment (as measured by the BASFI) was about 45% improved; spinal mobility as measured by the modified Schober's test, chest expansion, and occiput-to wall distance was improved by 19%, 33%, and 27%, respectively. These results corroborate similar improvements in physical function and spinal mobility seen in the 4-year extension (17) of the Davis *et al*. 24-week double-blind study(15) in subjects with AS. These sustained improvements in mobility and also function as measured by the BASFI contrast with the deterioration not uncommonly seen over time in this population (23).

Other components of the core set of assessments recommended in the most recent ASAS/EULAR recommendations (24) for the management of AS such as patient global assessment, stiffness, number of painful and number of swollen joints, and CRP had improvements similar to the BASFI results. Early responses seen within the original double-blind study or early in the first extension study were sustained through both extension studies indicating that etanercept is an effective therapy for the long-term management of patients with AS.

Although the open-label design may be

the best option for a study of this duration, it is a limitation because there is no placebo or comparator arm. Other limitations include its small sample size and the lack of radiographic assessment. Nevertheless, clinical assessments demonstrate a persistence of improved mobility, and patients continued to feel better and function better.

Together, the 3 studies (12-week double-blind study, and 2 long-term extensions) represent a total of 287.01 subject years, over 5 years of etanercept therapy. Etanercept at a dosage of 25 mg twice weekly continued to be well tolerated and improvements in disease symptoms including physical function and spinal mobility were sustained in this 3-year extension study. These results indicate that sustainable therapeutic benefit can be expected with etanercept in the long-term management of patients with ankylosing spondylitis.

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