Etanercept in Adult Patients with Early Onset Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To determine whether twice-weekly subcutaneous etanercept improves the signs and symptoms of adult patients with early onset ankylosing spondylitis (AS).

Methods. A retrospective analysis was performed on a subgroup of patients with AS with onset < 18 years of age from a multicenter, double-blind, placebo-controlled, randomized study of etanercept in the treatment of patients with AS. Twenty patients met criteria and are presented.

Results. As early as week four, 5/9 (56%) patients who received etanercept achieved an Assessments in Ankylosing Spondylitis 20% response (ASAS 20) versus only 1/11 (9%) of those who received placebo (p = 0.032). The observed ASAS 20 response continued through week 24, with 6/9 (66%) patients receiving etanercept responding, versus 2/11 of patients receiving placebo (p = 0.025).

Conclusion. Etanercept improves signs and symptoms of early onset AS in adult patients for at least 24 weeks. (J Rheumatol 2006;33:1634–6)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS
RECEPTORS
TNFR-FC FUSION PROTEIN
TUMOR NECROSIS FACTOR

Ankylosing spondylitis (AS) is a chronic inflammatory disease that affects the spine, peripheral joints, and other organ systems. Tumor necrosis factor (TNF) levels are elevated in serum[1,2] and in synovial tissue[3-5] of patients with AS, suggesting a role for TNF in the pathogenesis of the disease. Unfortunately, there is little published information about treatment options and safety concerns in a potentially unique patient subgroup with early onset. One case report indicated effectiveness of a TNF inhibitor in 2 patients with early onset disease[6].

Etanercept is a fusion protein that specifically binds TNF-α. Treatment with etanercept has resulted in significant and sustained improvement of clinical signs and symptoms of AS[7-11].

We examined a subgroup from a phase 3 trial of etanercept in AS to determine treatment efficacy in those with early onset disease.

MATERIALS AND METHODS

In this retrospective analysis, patients with early onset AS, defined as diagnosis of AS prior to 18 years of age, were identified from a phase 3 trial[7]. Of 277 patients in the trial, 20 fulfilled this criterion. All patients were at least 18 years of age at the time of trial entry.

The protocol for the double-blind, randomized, placebo-controlled phase 3 study of etanercept for the treatment of AS has been described[7]. Patients who met eligibility criteria were stratified by concomitant disease modifying antirheumatic drug (DMARD) usage and then randomly assigned to receive either placebo or etanercept 25 mg subcutaneously twice weekly (BIW) for 24 weeks. Efficacy and safety evaluations were performed at weeks 2, 4, 8, 12, and 24.

The primary efficacy endpoint was the proportion of patients achieving the Assessments in Ankylosing Spondylitis 20% response (ASAS 20) at 12 weeks[12].

All patients who received at least one dose of study drug were evaluated for efficacy and safety.

Statistical comparisons of the 2 treatment groups were made using the Mantel-Haenszel test with stratification for concomitant DMARD usage. All tests were 2-tailed with a 0.05 significance level.

RESULTS

While patients were not stratified by age of onset in the trial, there were no statistically significant differences in demographic and baseline disease characteristics of the 2 groups of early-onset patients (Table 1; all p values > 0.1). Both groups were primarily white, primarily male, and significantly younger than the overall trial population. All patients with HLA-B27 test results available were positive. Both groups of patients had longer disease duration, on average, than the total clinical trial population. Overall, measures of disease severity were generally similar in the 2 groups, although patients in the placebo group had slightly higher baseline Bath AS Disease Activity Index (BASDAI) and Functional Index (BASFI) (Table 1).

The placebo group also had a higher rate of prior DMARD use (6 had used at least one prior DMARD) than the etanercept group (3 had used at least one prior DMARD), as well as a higher average number of DMARD per patient (0.8 ± 1.2 vs 0.3 ± 0.7), though neither of these differences were statistically significant (p = 0.142 and p = 0.222, respectively). One

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Table 1. Demography and baseline disease characteristics of patients in the early onset etanercept and placebo subgroups, and in the adult onset trial population. All demography and disease characteristics, with the exception of age at onset, are summarized at the time blinded therapy was initiated. Values are number (%) unless otherwise indicated. There were no statistically significant differences between patients with early onset AS who received either etanercept or placebo.

	Early Onset AS, Placebo Group, n = 11	Early Onset AS, Etanercept Group, n = 9	Adult Onset Trial Population, n = 257
Male	9 (82)	6 (67)	195 (76)
Race			
Asian	1 (9)	0 (0)	5 (2)
Hispanic	1 (9)	0 (0)	8 (3)
White	9 (82)	9 (100)	239 (93)
Age, yrs, mean (SD)	29.8 (7.3)	33.4 (6.7)	42.8 (10.2)
Height, cm, mean (SD)	171.3 (8.4)	165.7 (8.7)	172.5 (9.9)
Weight, kg, mean (SD)	79.7 (18.6)	79.1 (17.8)	82.9 (19.1)
Disease duration, yrs, mean (SD)	14.5 (8.3)	17.8 (7.0)	9.8 (8.5)
Age at onset, mean (SD)	15.9 (1.6)	16.1 (2.2)	33.5 (10.3)
Patient global assessment, 0–100, mean (SD)	64.5 (24.7)	63.8 (17.2)	62.8 (18.0)
Back pain, 0–100, mean (SD)	56.6 (27.1)	62.1 (22.0)	62.6 (20.5)
BASFI, 0–100, mean (SD)	58.5 (18.8)	52.0 (15.7)	53.9 (21.1)
BASDAI, 0–100, mean (SD)	68.4 (20.8)	59.1 (28.4)	62.7 (21.2)
DMARD use at baseline	3 (27)	1 (11)	83 (32)

BASFI: Bath AS Function Index; BASDAI: Bath AS Disease Activity Index; DMARD: disease modifying antirheumatic drug.

patient receiving etanercept and 3 receiving placebo continued to take sulfasalazine during the trial. No patients receiving either placebo or etanercept had other concomitant DMARD usage, including methotrexate or hydroxychloroquine.

A statistically significantly higher proportion of patients receiving etanercept versus placebo showed an ASAS 20 response as early as week 4 (etanercept: 56%, placebo: 9%; p = 0.025). This difference was maintained at 12 and 24 weeks (Figure 1). Among patients receiving etanercept, the proportion of patients achieving ASAS 20 was similar at week 12 (59% of adult onset patients, 67% of early onset patients) and week 24 (56% of adult onset patients, 67% of early onset patients), despite the increased disease duration in the early onset population.

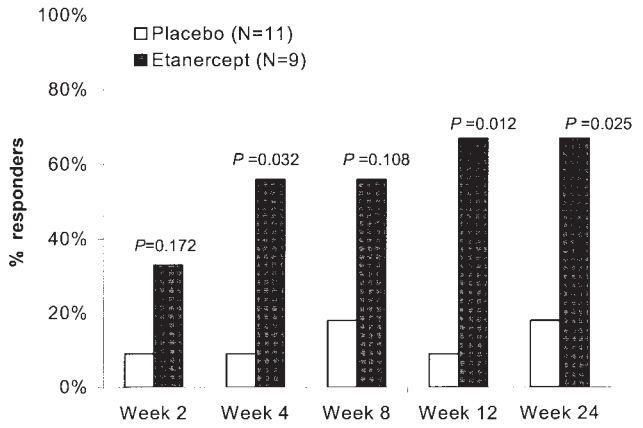

Figure 1. Proportion of ASAS 20 responders in adult patients with early onset AS.

Other measures of efficacy generally showed larger improvements among early onset patients who received etanercept, but did not attain statistical significance compared with the placebo group (Table 2), probably because of the small sample size. One exception: the occiput-to-wall measurement showed statistically significantly greater improvement among patients receiving etanercept versus placebo.

Adverse events occurred in similar proportions of patients receiving placebo (8/11) and etanercept (7/9); this is similar to the proportions of patients who experienced adverse events in the overall trial population. No serious adverse events were reported, but a single grade 3 adverse event (a grand mal seizure) was reported in a patient taking etanercept, who reported having discontinued lorazepam and pain medications prior to the seizure. This event was not considered by the investigator to be related to study drug; although study drug was temporarily suspended, the patient subsequently returned to etanercept, completed the study, and enrolled in the ongoing open-label trial. Two patients receiving etanercept and none receiving placebo reported injection site reactions; the only other events occurring in more than 1 patient were headaches (5 etanercept; 0 placebo) and injection site bruising (4 etanercept, 0 placebo).

Most early onset adult patients from both groups were admitted into an ongoing open-label extension study of 25 mg etanercept BIW, which will yield insight into the extended safety and efficacy of etanercept in this patient population.

Table 2. Assessment of disease improvement in the 2 groups receiving placebo or etanercept.

	Placebo n = 11	Etanercept n = 9	p
ASAS 50 responders, n (%)	2/11 (18)	4/9 (44)	0.143
ASAS 70 responders, n (%)	1/11 (9)	3/9 (33)	0.172
ASAS partial remission, n (%)	1/11 (9)	3/9 (33)	0.172
BASDAI, mean % change from baseline (SE)	10.9 (15.4)	47.6 (11.9)	0.116
BASFI, mean % change from baseline (SE)	1.7 (15.7)	44.5 (12.7)	0.077
Chest expansion, mean change from baseline (SE)	–0.26 (0.39)	0.20 (0.68)	0.386
Modified Schober's, mean change from baseline (SE)	0.40 (0.34)	0.74 (0.44)	0.796
Occiput-to-wall, mean change from baseline (SE)	0.45 (0.56)	–1.87 (1.00)	0.021

DISCUSSION

Recent evidence has indicated that early onset AS has a higher rate of disability than adult onset AS[13]. In addition, there is a longer delay in diagnosis in patients with early onset AS than in their adult counterparts. These factors lend a sense of urgency to timely and accurate diagnosis of these young patients and to early institution of effective therapies.

Our study represents a secondary analysis, and the placebo and etanercept populations are slightly but not statistically significantly different in baseline demographics and disease severity. Thus, these results cannot be considered definitive. However, this study does suggest that administration of 2 weekly doses of etanercept improves signs and symptoms in adult patients with early onset AS for up to 24 weeks. Given the dearth of literature examining therapeutic options in this important subgroup of patients, the apparent efficacy of etanercept is noteworthy.

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REFERENCES

1. Toussirot E, Lafforgue P, Boucraut J, et al. Serum levels of interleukin 1-beta, tumor necrosis factor-alpha, soluble interleukin 2 receptor and soluble CD8 in seronegative spondylarthropathies. Rheumatol Int 1994;13:175-80.
2. Gratacos J, Collado A, Filella X, et al. Serum cytokines (IL-6, TNF-alpha, IL-1 beta and IFN-gamma) in ankylosing spondylitis: a close correlation between serum IL-6 and disease activity and severity. Br J Rheumatol 1994;33:927-31.
3. Braun J, Bollow M, Neure L, et al. Use of immunohistologic and in situ hybridization techniques in the examination of sacroiliac joint biopsy specimens from patients with ankylosing spondylitis. Arthritis Rheum 1995;38:499-505.
4. Canete JD, Llena J, Collado A, et al. Comparative cytokine gene expression in synovial tissue of early rheumatoid arthritis and seronegative spondyloarthropathies. Br J Rheumatol 1997;36:38-42.
5. Grom AA, Murray KJ, Luyrink L, et al. Patterns of expression of tumor necrosis factor alpha, tumor necrosis factor beta, and their receptors in synovia of patients with juvenile rheumatoid arthritis and juvenile spondylarthropathy. Arthritis Rheum 1996;39:1703-10.
6. Schmeling H, Horneff G. Infliximab in two patients with juvenile ankylosing spondylitis. Rheumatol Int 2004;24:173-6.
7. Davis JC Jr, van der Heijde DM, Dougados M, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum 2003;48:3230-6.
8. Cohen J. Clinical and laboratory improvement in ankylosing spondylitis after treatment with etanercept: a case report. J Clin Rheumatol 2000;6:221-4.
9. Marzo-Ortega H, McGonagle D, O'Connor P, Emery P. Efficacy of etanercept in the treatment of the entheseal pathology in resistant spondylarthropathy: a clinical and magnetic resonance imaging study. Arthritis Rheum 2001;44:2112-7.
10. Gorman JD, Sack KE, Davis JC, Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. N Engl J Med 2002;346:1349-56.
11. Brandt J, Khariouzov A, Listing J, et al. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. Arthritis Rheum 2003;48:1667-75.
12. Anderson JJ, Baron G, van der Heijde D, Felson DT, Dougados M. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. Arthritis Rheum 2001;44:1876-86.
13. Stone M, Warren RW, Bruckel J, Cooper D, Kurtinecz M, Inman RD. Juvenile-onset ankylosing spondylitis is associated with worse functional outcomes than adult-onset ankylosing spondylitis. Arthritis Care Res 2005;53:445-51.