The role of etanercept in ankylosing spondylitis

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ABSTRACT

Ankylosing spondylitis is a chronic inflammatory disease that leads to significant loss of function and disability in patients. Current conventional therapies have not demonstrated improvement in axial symptoms and progressive ankylosis of the spine. The use of new biologic agents that block the actions of tumor necrosis factor-alpha have, for the first time, reported significant improvement in axial symptoms and reduction in spinal inflammation in short-term studies. Future studies with larger numbers of patients over long periods of time will eventually determine the long-term success and safety of these agents.

Introduction

Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine implicated in playing a central role in the pathogenesis of a number of inflammatory processes. Recent observations from animal models also suggest that TNF-α may play a role in multiple autoimmune diseases. Transgenic mice expressing modified human TNF-α develop a clinical picture resembling human rheumatoid arthritis (RA), and mice expressing a truncated form of the TNF-α gene from the white-footed mouse develop a syndrome closely resembling human ankylosing spondylitis (AS), with axial involvement and subsequent vertebral end plate destruction and fusion (1, 2). These observations suggest that TNF-α may play a causative role in the spondyloarthropathies.

Results from human studies also support the involvement of TNF-α in AS and the other seronegative spondyloarthropathies. Levels of serum TNF-α have been reported to be significantly higher in patients with AS than in patients with non-inflammatory back pain (3), and a trend toward higher serum TNF-α in AS patients as compared with healthy controls has been noted (4). High levels of TNF-α mRNA have been found in the peripheral and axial joint synovia of patients with RA, spondyloarthritis (SpA), juvenile SpA, and AS (5-7).

Etanercept (TNFR:Fc; ENBREL®) is a soluble fusion protein comprising an epitope derived from the p75 tumor necrosis factor receptor fused to the Fc portion of IgG (Fig. 1). It has been shown to bind TNF with high affinity and to block the effects of TNF-α in model systems.

In several multicenter, double-blind, placebo-controlled studies, etanercept has been shown to improve the signs and symptoms of RA and to be effec-

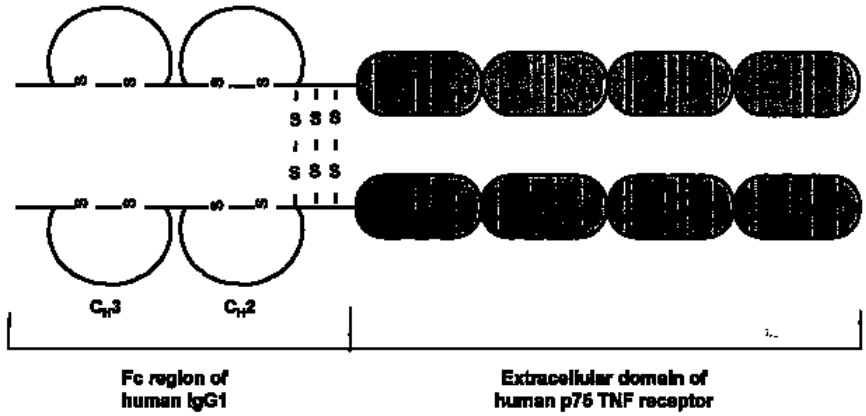

Fig. 1. Schematic diagram of etanercept.
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tive in treating the joint and skin manifestations of psoriatic arthritis (PsA), a seronegative spondyloarthopathy (8-11). Preliminary reports from open label and placebo-controlled studies suggest that TNF blockers may be effective in other seronegative spondyloarthropathies, such as reactive arthritis, resistant spondyloarthropathy, undifferentiated spondyloarthropathy, refractory juvenile ankylosing spondylitis, and ankylosing spondylitis (12-16).

A recent study using Etanercept in patients with spondylitis demonstrated significant clinical efficacy (13). This study also reported a decrease in inflammation of the peripheral arthritis, the spine, and the sacroiliac joint after several months of therapy by MRI. At the end of the study 86% of the patients treated had resolution or improvement in MRI sites of inflammation (13). These encouraging preliminary reports suggest that TNF-α blockade could be associated with regression of inflammation and have potential implications for the progression of long-term structural damage associated with the disease.

Based on (1) the animal models, (2) elevated levels of the cytokine in patients, (3) encouraging results of reduced radiographic inflammation, and (4) the success in related autoimmune diseases, we undertook a randomized double-blind, placebo-controlled study to evaluate the safety and efficacy of Etanercept in patients with AS (16).

In a recent study, we enrolled 40 patients with AS in a 4-month, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Etanercept, 25 mg, delivered SC twice weekly. Inclusion criteria were: (1) a diagnosis of AS as defined by the modified New York Clinical Criteria for definite AS, and (2) active disease; defined as morning stiffness of 45 minutes or more, inflammatory back pain, and patient and physician global assessments of disease of moderate or higher. Patients continued stable doses of non-steroidal anti-inflammatory drugs (NSAIDS), corticosteroids, or disease modifying anti-rheumatic drugs (DMARDs) during the trial. Patients were excluded if they had other forms of spondylitis other than AS or complete spinal fusion.

The primary endpoint of the study was the proportion of patients who responded to treatment in the etanercept group vs. the placebo group. To be considered responders, patients had to demonstrate at least 20% improvement from baseline in at least 3 of the following 5 outcome measures recommended by the Assessments in Ankylosing Spondylitis Working Group (17): morning stiffness, spinal pain, function, patient global assessment of disease, and swollen joint score, with one being morning stiffness or spinal pain, and without worsening in any of these symptoms. Multiple secondary measures of efficacy were also evaluated. [The study analysis used intention-to-treat principles with the last available assessment for each patient carried forward.]

Baseline demographic and clinical characteristics of the patients are summarized in Table I. Groups were similar in terms of race, proportion of patients who were HLA-B27 positive, age, duration of disease, and concomitant medicines. Several measures suggest that the Etanercept group may have had more severe disease at the start of the trial: physical function was significantly poorer in the Etanercept group (judged by responses on Medical Outcomes Study Short-Form Health Survey [SF-36], more Etanercept patients were receiving second-line therapies (steroids and/or DMARDs), and erythrocyte sedimentation rate (ESR) was higher.

Over the course of the study, 3 patients withdrew: 1 from the Etanercept group, for reasons unrelated to the study, and 2 from the placebo groups for lack of efficacy.

The primary endpoint of this study, the proportion of patients achieving a response at Day 112, was significantly higher in the group of patients treated with Etanercept (75%) than in those treated with placebo (40%). (Table II, Fig. 2) The response to etanercept occurred as quickly as one month and did not diminish over the course of the study.

In addition, improvements were seen in a number of secondary outcome

Table I. Baseline demographics of subjects.

Characteristic[1]	Etanercept n=20	Placebo n=20
Male sex (%)	65	90
Caucasian (%)	75	70
HLA-B27+ (%)	95	90
Mean age (yr)	38 ± 10	39 ± 10
Mean duration of AS (yr)	15 ± 10	12 ± 9
Concomittant medications		
NSAIDs (%)[2]	80	95
Steroids (%)	25	10
DMARDs (%)[3]	40	35
Multiple medications for AS (%)	45	35
Clinical features		
Duration of morning stiffness (min)	90.0 ± 50.6	60.0 ± 70.7
Modified Schober's test (cm)	12.5 ± 1.5	13.5 ± 1.5
Patient global assessment[4]	3.0 ± 0.7	3.0 ± 0.7
Physician global assessment[5]	54.5 ± 19.6	48.0 ± 16.4
Erythrocyte sedimentation rate (mm/hr)	34.5 ± 23.1	20.0 ± 16.3

[1] Plus-minus values are median values ± SD; differences between groups were all not statistically significant.
[2] NSAIDs denotes nonsteroidal antiinflammatory drugs
[3] DMARDs denotes disease-modifying antirheumatic drugs.
[4] Scores can range from 0 (no disease) to 5 (most severe).
[5] Scores can range from 0 to 100 mm on a visual analogue scale with 100 mm indicating most severe disease.

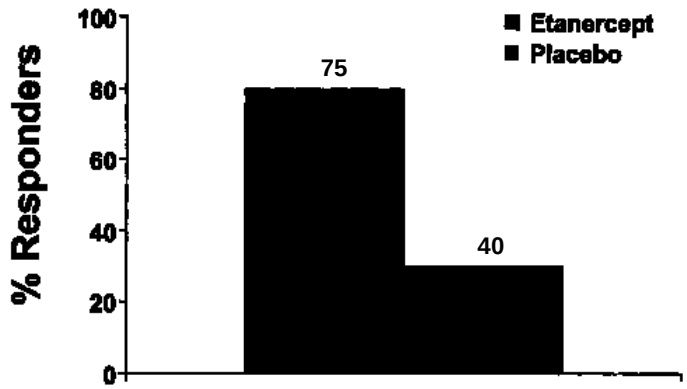

Fig. 2. Percent of patients considered responders at month 4 ($p < 0.01$).

Table II. Primary outcomes month 41.

	Etanercept n=20	Placebo n=20	P[2]
Number (%) of responders[3]	15 (75)	8 (40)	0.01
Duration of morning stiffness (min)			
Baseline	90.0 ± 50.6	60.0 ± 70.7	0.12
Day 112	25.0 ± 78.9	60.0 ± 65.0	< 0.0001
Nocturnal spinal pain[4]			
Baseline	65.0 ± 23.9	46.5 ± 25.3	0.32
Day 112	15.0 ± 24.3	38.0 ± 27.8	< 0.0001
BASFI[5]			
Baseline	4.5 ± 2.1	3.2 ± 2.5	0.06
Day 112	2.2 ± 2.1	3.1 ± 3.0	< 0.0001
Patient global assessment[6]			
Baseline	3.0 ± 0.7	3.0 ± 0.7	0.33
Day 112	2.0 ± 0.6	3.0 ± 0.9	< 0.001
Swollen joint score[7] (mean)			
Baseline	3.7 ± 8.1	3.2 ± 5.3	0.53
Day 112	1.6 ± 3.8	3.7 ± 7.6	0.17

[1]Plus-minus values are median values ± SD; [2]p values calculated by Mann-Whitney t-tests; [3]p value calculated by Fisher's exact test; [4]Pain (100 mm VAS): 0, none; 100, most severe; [5]Functional limitations (0-10): 0, none; 10, completely limited; [6]Disease activity (0-5): 0, no disease activity; 5, very severe; [7]Peripheral joint count of 66 joints on 4 point swelling scale (0, none; 1, mild; 2, moderate; 3, severe).

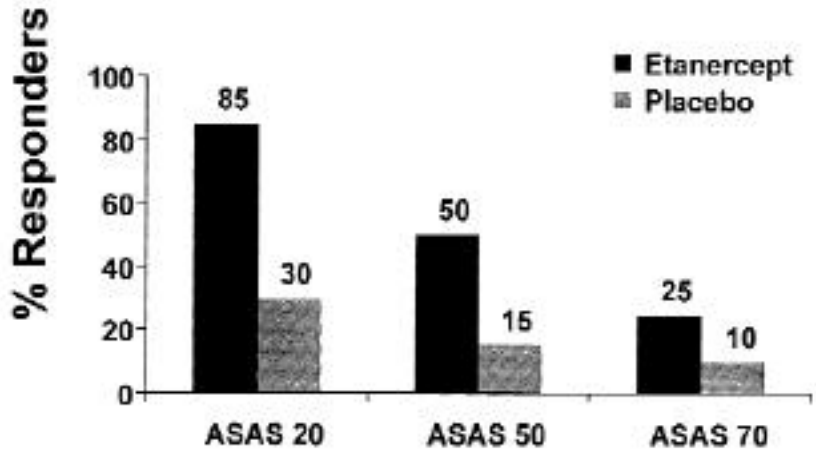

Fig. 3. Percent of patients achieving ASAS 20, 50 and 70.

measures (Table III; measures in bold were components of the definition of "response" used to evaluate the primary endpoint). Function, stiffness, global assessments of disease, and signs of peripheral disease had all improved significantly by the 4th month of the trial, and benefit continued through the end of the study. Measures of spinal mobility showed a less dramatic response than other measures at 4 months, but both chest expansion and occiput-to-wall measurements continued to improve with longer drug treatment, suggesting that the spinal response takes longer to develop. Quality of life, assessed using the SF-36, also improved in patients treated with etanercept (data not shown). Although the ASAS response criteria were not published at the time of the study, post-hoc analysis demonstrated significant improvement of the ASAS 20, ASAS 50 and ASAS 70 response measures (Fig. 3) (18).

There were no serious adverse events or withdrawals due to adverse events and there were no statistically significant differences in the adverse events observed between the treatment groups. The most common adverse events in the blinded trial consisted of self-limited injection-site reactions (5 patients in the etanercept group; one patient in the placebo group) and minor uncomplicated infections (10 patients in the etanercept group; 12 patients in the placebo group) that occurred at comparable rates between the two treatment groups.

Two neurologic events were reported in a single patient treated with etanercept. The patient experienced tinnitus, which lasted for 3 days and resolved spontaneously, and later, an increased frequency of pre-existing muscle fasciculation. Neurologic and laboratory examinations were normal. Study medication was held pending complete neurologic consultation and evaluation. No abnormality was noted on any of the evaluations, and the patient was diagnosed with benign fasciculations. The frequency of the patient's symptoms returned to baseline and remained at this level with the re-initiation of study medication.

Table III. Secondary outcomes at month 4.[1]

	Etanercept n=20	Placebo n=20	P[2]
Spinal pain[3]			
Baseline	62.0 ± 21.3	49.0 ± 24.5	0.23
Day 112	23.5 ± 28.5	39.5 ± 28.5	0.0003
Physician global assessment[4]			
Baseline	54.5 ± 19.6	48.0 ± 16.4	0.29
Day 112	23.0 ± 10.6	55.5 ± 22.7	< 0.0001
Dougados Functional Index[5]			
Baseline	18.0 ± 6.1	12.0 ± 6.8	0.11
Day 112	8.0 ± 7.4	10.0 ± 8.3	0.004
Modified Newcastle Enthesis Index[6]			
Baseline	4.5 ± 8.4	3.0 ± 7.9	0.72
Day 112	0.0 ± 3.0	1.5 ± 8.0	0.001
Swollen joint count[7] (mean)			
Baseline	3.3 ± 7.1	2.6 ± 4.5	0.61
Day 112	1.5 ± 3.8	2.9 ± 6.1	0.16
Tender joint count[7]			
Baseline	3.0 ± 6.8	2.0 ± 9.4	0.60
Day 112	1.0 ± 1.8	2.0 ± 14.4	0.07
Tender joint score[7]			
Baseline	3.5 ± 10.5	2.5 ± 11.8	0.40
Day 112	1.0 ± 2.5	2.5 ± 23.1	0.07
ESR (mm/hr)			
Baseline	34.5 ± 23.1	20.0 ± 16.3	0.07
Day 112	8.5 ± 12.8	16.5 ± 18.7	< 0.0001
Fatigue Severity Scale[8]			
Baseline	4.6 ± 1.6	4.3 ± 1.5	0.32
Day 112	4.2 ± 1.6	4.4 ± 1.6	0.89
Chest expansion (cm)			
Baseline	2.6 ± 1.6	3.1 ± 1.7	1.00
Day 112	3.5 ± 1.9	2.9 ± 1.7	0.006
Modified Schober's test (cm)			
Baseline	12.5 ± 1.5	13.5 ± 1.5	0.13
Day 112	13.4 ± 1.6	13.4 ± 1.5	0.26
Occiput-to-wall measurement (mean cm)			
Baseline	5.7 ± 7.9	2.0 ± 1.5	0.26
Day 112	4.7 ± 7.6	2.7 ± 4.4	0.11

[1]Plus-minus values are median values ± SD.
[2]p values calculated by Mann-Whitney t-tests.
[3]Pain without time restrictions (100 mm VAS): 0, none; 100, severe.
[4]Disease activity (100 mm VAS): 0, none; 100, severe.
[5]Functional limitations (0-40): 0, none; 40, completely limited.
[6]Seventeen entheses on a 4 point scale (0, none; 1, mild; 2, moderate; 3, severe).
[7]Peripheral joint count of 66 joints on 4 point pain scale (0, none; 1, mild; 2, moderate; 3, severe).
[8]Fatigue Severity Scale (0-7)

Conclusions

The encouraging results from this trial (and others reviewed in this volume) suggest that TNF blocking therapies may be effective and safe treatments for AS, and may offer distinct advantages over commonly used therapies. NSAIDs only treat the pain of the disease, and few double-blind, placebo-controlled studies of other DMARDs have been done in patients with AS. No currently used therapy has been shown to improve axial symptoms of AS. The current trial supplies evidence that etanercept can be of benefit even to patients with long duration of disease (mean disease duration 15 years in patients initially randomized to receive etanercept) and with moderate to severe disease. Patients treated with etanercept demonstrated evidence of improvement in not only the pain associated with AS, but also showed increased function and quality of life, and had improvement in the axial symptoms of the disease. Etanercept was also safe in conjunction with other AS medications.

This study was designed to determine the short-term efficacy of etanercept in AS. Although benefit was sustained throughout the trial, the long-term effects of etanercept treatment in AS have not yet been studied. Etanercept has been shown to slow the radiographic progression of RA, and evidence from MRI scans collected as part of a 6-month open-label descriptive study (13) suggests that etanercept may indeed help control entheseal lesions in patients with AS. Further research will evaluate the long-term safety and efficacy of etanercept (and other TNF inhibitors) in AS and the effects of these drugs on the peripheral and axial radiographic progression of the disease.

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