

Short-Term Trial of Etanercept in Behçet's Disease: A Double Blind, Placebo Controlled Study

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ABSTRACT. Objective. To determine the effect of the tumor necrosis factor- α blocker etanercept on the pathergy and monosodium urate (MSU) status and on the mucocutaneous and articular manifestations of patients with Behçet's disease (BD).

Methods. Forty male patients with BD, all with positive pathergy and MSU tests and mucocutaneous disease and/or arthritis, were randomized (20 patients to each study arm) to receive either etanercept 25 mg twice a week or placebo for 4 weeks. The pathergy and MSU responses and the frequencies of mucocutaneous and articular manifestations were compared between the 2 groups.

Results. There were no decreases in the pathergy and MSU responses in the etanercept group compared to the placebo group at any time. The mean numbers of oral ulcers, nodular lesions, and papulopustular lesions were less in the etanercept group compared to the placebo group at all weekly evaluations, except for the second week for papulopustular lesions. The probability of being free of oral ulcers and nodular lesions was also significantly higher in the former group (log-rank chi-square = 9.83, $p = 0.0017$; log-rank chi-square = 14.17, $p = 0.0002$, respectively).

Conclusion. Etanercept did not affect the pathergy reaction and the cutaneous response to MSU crystals. However, the drug was effective in suppressing most of the mucocutaneous manifestations of BD. (J Rheumatol 2005;32:98–105)

Key Indexing Terms:

BEHÇET'S DISEASE

THERAPY

ETANERCEPT

Oral and genital ulcerations, erythema nodosum, papulopustular skin eruptions, arthritis, uveitis, cerebritis, deep vein thrombosis (DVT), and arterial aneurysms are the hallmarks of Behçet's disease (BD)¹. A T cell mediated immune response seems to be important in the pathogenesis of BD². CD4+ T lymphocytes seem to be the major cell type in inflammatory infiltrates, and increased concentrations of tumor necrosis factor- α (TNF- α) and interferon- γ (IFN- γ) have been described^{3,4}. Data on the clinical effects of TNF- α blockers in BD, however, have been scarce. Case reports suggest that the TNF- α blocker infliximab is beneficial in patients with BD with mucocutaneous^{5,6}, ocular^{7,8}, and gastrointestinal (GI) involvement^{9,10}.

The skin pathergy reaction of BD is a manifestation of the increased inflammatory response to trauma or to non-specific stimuli, and it is not limited only to the skin², sug-

gesting a role in disease pathogenesis. A positive test is defined as the formation of a papule or pustule at an intradermal needle insertion site at 48 h. It has a sensitivity of ~50% and a specificity of ~98%. However, it has limited reproducibility¹¹. The presence of T cell, monocyte, and macrophage infiltration and the expression of IFN- γ and interleukin 12 (IL-12) suggest a Th1-type immune response in its pathogenesis¹².

Skin hyperreactivity in BD can also be induced by the intradermal injection of monosodium urate (MSU) crystals¹³. A positive MSU test is defined as a persistent area of erythema at the injection site at 48 h. It has a sensitivity of 61–78% and a specificity of 94–100%^{13,14}. No information is available about its immune histology.

We evaluated the effect of the TNF- α blocker etanercept on the pathergy and MSU reactions along with the mucocutaneous manifestations and/or arthritis in patients with BD, in a double blind, placebo controlled trial.

MATERIALS AND METHODS

Study design. This was a 4 week, randomized, double blind, placebo controlled trial conducted at the Behçet's Syndrome Research Center, Cerrahpasa Medical Faculty, Istanbul, a multidisciplinary outpatient clinic operating since 1977. The study protocol was developed solely by the investigators and was approved by the faculty ethics committee. All eligible patients signed an informed consent form at their screening visits.

Patients. All patients fulfilled the criteria of the International Study Group for the diagnosis of BD¹⁵. Inclusion criteria were (1) male sex; (2) age 18–45 years; (3) the presence of at least one of the following clinical man-

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Supported by Wyeth Pharmaceuticals, Philadelphia, PA, USA.

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Submitted February 3, 2004; revision accepted August 30, 2004.

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ifestations within the preceding 3 months of study entry: (a) one episode of oral ulcer, (b) genital ulcer, (c) nodular lesion (erythema nodosum or superficial thrombophlebitis), (d) a swollen joint; and (4) a positive pathergy and a MSU test.

Initially a chart review of the patients who had been registered between 1998 and 2001 was done to determine patients who currently had active mucocutaneous lesions and/or arthritis. Those patients who could be reached were invited for a second evaluation. Pathergy and MSU tests were done in those who fulfilled the clinical criteria (Figure 1).

Pathergy positivity was defined as the formation of a papule or pustule 48 h after the insertion of a 20 gauge needle into the patient's forearm. MSU positivity was described as an area of erythema that formed after subcutaneous injection of 2.5 mg MSU crystals suspended in saline into the contralateral forearm, again at 48 h. The size of the erythema was measured by marking its circumference, transferring it to metric graph paper, and calculating the area. The recruitment period was 24 months. Eighteen patients who were using colchicine (11 in the etanercept and 7 in the placebo arms) and 5 patients who were using azathioprine (all in the placebo arm) due to resistant mucocutaneous lesions, stopped their medications and underwent a washout period of 4 weeks before entering the trial. However, 2 patients in the etanercept arm (one with a recent exacerbation of DVT and one with painful arthritis) and one in the placebo arm (again with a recent exacerbation of DVT) did not undergo this washout period as they were judged to have relatively severe disease. They continued to use azathioprine or corticosteroids throughout the study.

Exclusion criteria were the presence of serious organ involvement such

as eye and central nervous system and major arterial disease, systemic or local infection including a history of tuberculosis, the use of the study drug during the 4 weeks prior to study entry, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values 2 times above the normal limits, a hematocrit of < 28%, white blood cell (WBC) count < 4000/mm³, platelet count < 140,000/mm³, and a serum creatinine of > 1.9 mg/dl.

Randomization. Equal numbers of cards assigned to either the active drug or the placebo arm (20 for each arm) were mixed, drawn, and placed sequentially on a list. The code was opened only after all data had been entered into the computer for analysis.

Study drug administration. Etanercept 25 mg vials and the placebo vials were prepared by Wyeth Ayerst Pharmaceuticals. The characteristics of the study drug and placebo vials were identical and the clinical assessors and patients were blinded to the preparation being administered. Vials were distributed to patients by a study nurse who was not blinded.

Both the drug and the placebo were dissolved in 1 ml distilled water and were injected subcutaneously, 2 times a week. The first injection in each week was administered by the study nurse, the second was performed at a local clinic situated near the patient's home. All used vials were collected and counted.

Clinical evaluation. The pathergy and MSU tests were performed at the initial visit (before study drug or placebo was administered), at Weeks 1 and 4, and at the third month after the trial ended. The test results were assessed by a rheumatologist.

The 3 month post-study evaluation was arbitrarily set to assess post-trial disease flares.

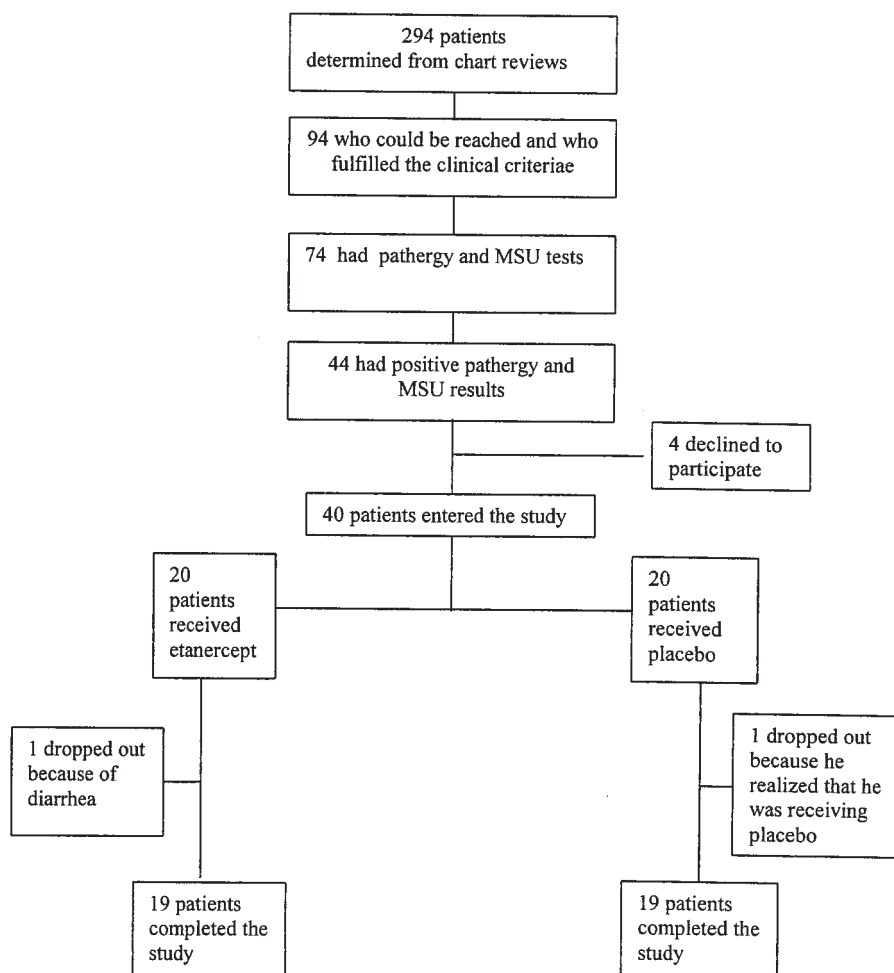


Figure 1. Outcome of treatment randomization and followup of the patients.

Patients were evaluated at baseline, at Weeks 1, 2, 3 and 4, and at the third month after the trial ended. The actual number of oral and genital ulcers, nodular lesions, and joints with arthritis were recorded at each visit. The numbers of follicular lesions were graded semiquantitatively as 0: no lesions, 1: 1–5 lesions, 2: 6–15 lesions and 3: > 15 lesions. The clinical assessments throughout the study were done by 2 rheumatologists, a dermatologist, and an ophthalmologist.

Safety evaluation. Vital signs were recorded at each visit. Complete blood counts, serum creatinine, ALT, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) measurements and an electrocardiography were obtained at study entry, at Week 4, and at the third month after the completion of the study. Patients were additionally questioned for any adverse effects at each visit.

Statistical analysis. The primary endpoints of the study were the amount of suppression of the pathergy response and MSU tests with etanercept. The secondary endpoints were the differences between the mean number of mucocutaneous lesions and swollen joints between the 2 study arms at each weekly visit, and the probabilities of being free of oral ulcers, genital ulcers, papulopustular lesions, nodular lesions, and arthritis during the entire study period.

The analyses were performed on the basis of intent-to-treat. All the clinical indicators were based on data obtained by the physicians at weekly clinical visits.

Comparisons of the baseline demographic data were by Student t tests and chi-square tests. The areas of erythema induced by MSU at study entry and at 3 months after the study in the etanercept and placebo arms were compared by paired Student t test. Differences between the continuous variables in the etanercept and placebo groups were analyzed by Mann-Whitney U test, whereas dichotomous variables were evaluated by Fisher's exact test.

The time-dependent distribution of the clinical manifestations and the probability of being symptom-free were evaluated by Kaplan-Meier plots with the log-rank test.

RESULTS

Study population. Forty patients entered the trial. Thirty-eight patients completed the 4 week study (Figure 1). There were no significant differences at baseline between the ages, the disease durations, and the clinical findings among the 2 groups (Table 1).

One patient in the etanercept arm dropped out because of an episode of diarrhea and one patient in the placebo arm left the study because he realized that he was using placebo due to a misplaced label on his vial.

Compliance rates calculated from the returned vials were 96% in the etanercept group and 98% in the placebo group.

Pathergy and MSU tests. The results of the pathergy and MSU tests in the etanercept group were available in 18/20 patients at Week 1, in 19/20 patients at Week 4, and in 19/20 patients at the third month after the study. These data were 20/20, 19/20, and 19/20 for the placebo group.

The frequency of pathergy positivity did not differ significantly between the etanercept and placebo groups at any time (Table 2).

The mean area of erythema induced by MSU in the placebo group was significantly less than in the etanercept group at Week 1: 2086 mm² (95% CI 1457–2716) vs 3057 mm² (95% CI 2276–3839) (p = 0.039). This difference did not persist at Week 4 and at the third month after the end of the study (Table 2).

It was also noted that the mean areas of erythema induced by MSU in both study arms were lower at the end of the third month compared to study entry: 2731 mm² (95% CI 1706–3756) vs 1587 mm² (95% CI 974–2199) (p = 0.08) for the etanercept arm and 2913 mm² (95% CI 2440–3386) vs 1969 mm² (95% CI 1276–2661) (p = 0.02) for the placebo arm.

Oral ulcers. The mean numbers of oral ulcers were significantly less in the etanercept group compared to the placebo group at Weeks 1, 2, 3, and 4. This difference disappeared at the post-study period and the mean values in both groups returned to pretreatment levels (Table 2). It was seen that 45% (9/20) of the patients receiving etanercept were free of oral ulcers at the end of the study compared to 5% (1/20) of

Table 1. Patient characteristics at baseline.

	Etanercept, n = 20	Placebo, n = 20	p
Age, yrs	28.5 ± 5.3	30.8 ± 6.2	0.22
Disease duration, yrs	2.8 ± 2.6	4.3 ± 3.2	0.10
Oral ulceration	2.0 ± 1.3	1.8 ± 1.6	0.67
Genital ulcers	1.3 ± 1.5	0.8 ± 1.3	0.31
Papulopustular lesions*	1.6 ± 1.4	1.7 ± 0.9	0.89
Nodular lesions	1.1 ± 1.5	2.0 ± 3.3	0.29
No. of swollen joints	0.5 ± 0.8	0.4 ± 0.8	0.70
Deep vein thrombosis** (%)	3 (15)	4 (20)	1.00
Pathergy positivity, %	100	100	NA
Monosodium urate***	2731 ± 2190	2913 ± 1009	0.73
ESR, mm/h	33.3 ± 19.3	25.3 ± 23.3	0.26
CRP, mg/dl	3.4 ± 3.5	3.5 ± 4.2	0.96
Colchicine withdrawal (%)	11 (55)	7 (35)	0.34
Azathioprine withdrawal (%)	0	5 (20)	0.05

Data are mean ± SD or number of patients (%). * Data on papulopustular lesions represent semiquantitative scores. ** Deep vein thrombosis of the lower extremities. *** Area of erythema in mm². Mean values were compared with the Student T test, frequencies were compared with the chi-square test.

Table 2. Results of the pathology and MSU tests and mean number of lesions (95% CI) in the etanercept and placebo groups.

	Week 0		Week 1		Week 2		Week 3		Week 4		3 months after trial	
	ETAN	PLA	ETAN	PLA	ETAN	PLA	ETAN	PLA	ETAN	PLA	ETAN	PLA
Pathergy positivity	20/20	20/20	6/18	11/20	—	—	—	—	6/19	8/19	8/19	8/19
MSU, mm ²	2731 (1706–3756)	2913 (2440–3386)	3057 ⁿ (2276–3839)	2086 ⁿ (1457–2716)	—	—	—	—	2786 (1623–3949)	2355 (1411–3299)	1587 (974–2199)	1969 (1276–2661)
Oral ulcers	2.00 (1.37–2.62)	1.80 (1.05–2.55)	0.35 ^a (0.03–0.73)	1.60 ^a (0.83–2.37)	0.50 ^b (0.18–0.82)	1.30 ^b (0.84–1.76)	0.35 ^c (0–0.70)	1.58 ^c (0.74–2.42)	0.79 ^d (–0.50–1.63)	1.47 ^d (0.77–2.18)	2.00 (1.15–2.85)	1.58 (0.82–2.34)
Genital ulcers	1.20 (0.56–1.94)	0.80 (0.20–1.40)	0.40 (–0.23–1.03)	0.30 (–0.04–0.64)	0 (–0.40–1.50)	0.55 (–0.40–1.50)	0 (–0.40–1.50)	0.05 (–0.06–0.16)	0 (–0.06–0.16)	0.05 (–0.06–0.16)	0.60 (–0.25–1.45)	0.37 (–0.30–1.03)
Nodular lesions	1.15 (0.45–1.85)	2.00 (0.47–3.57)	0.40 ^e (–0.07–0.87)	1.35 ^e (0.65–2.05)	0.50 ^f (–0.05–1.05)	1.75 ^f (0.80–2.70)	0 ^g (–0.40–1.50)	1.26 ^g (0.24–2.29)	0.05 ^h (–0.06–0.16)	1.37 ^h (0.39–2.35)	1.45 (0.14–2.76)	0.32 (–0.07–0.71)
Papulopustular lesions	1.60 (0.95–2.25)	1.65 (1.24–2.06)	1.05 ^j (0.42–1.68)	1.75 ^j (1.27–2.23)	1.05 (0.66–1.44)	1.55 (0.99–2.11)	0.80 ^k (0.33–1.27)	1.79 ^k (1.20–2.38)	0.89 ^m (0.30–1.49)	1.53 ^m (0.96–2.00)	1.60 (1.16–2.04)	1.16 (0.76–1.56)
Swollen joints	0.45 (0.06–0.84)	0.35 (–0.03–0.73)	0.10 (–0.10–0.31)	0.30 (–0.01–0.51)	0.10 (–0.11–0.31)	0.30 (–0.07–0.61)	0.11 (–0.12–0.33)	0.37 (–0.03–0.77)	0.11 (–0.12–0.33)	0.21 (–0.09–0.51)	0.79 ^p (0.20–1.38)	0.10 ^p (–0.12–0.33)

ETAN: etanercept; PLA: placebo; MSU: Monosodium urate; U: Mann-Whitney U test. ^a U = 102.5, p = 0.007; ^b U = 102.5, p = 0.01; ^c U = 103.5, p = 0.04; ^d U = 109.5, p = 0.04; ^e U = 114, p = 0.02; ^f U = 95.5, p = 0.004; ^g U = 110, p = 0.02; ^h U = 111, p = 0.04; ⁱ U = 108, p = 0.01; ^k U = 100, p = 0.01; ^m U = 118.5, p = 0.07; ⁿ U = 103.5, p = 0.04; ^p U = 140.0, p = 0.02.

the placebo group (log-rank chi-square = 9.83, p = 0.0017; Figure 2A). Significant differences between the 2 study arms started at Week 1.

Genital ulcers. There were no differences between the mean numbers of genital ulcers among the etanercept and placebo groups at any timepoint in the study (Table 2). Similarly, there were also no differences in the probabilities of being genital ulcer-free between the 2 groups [85% (17/20) in the etanercept group vs 70% (14/20) in the placebo group (log rank chi-square = 1.18, p = 0.28)].

Nodular lesions. The mean number of nodular lesions in the etanercept group was significantly less than the mean num-

ber of lesions in the placebo group at Weeks 1, 2, 3, and 4. This difference disappeared at the third month after the study (Table 2). Life table analysis revealed that 85% (17/20) of patients receiving etanercept were free of nodular lesions at the end of the study compared to 25% (5/20) of the placebo group (log-rank chi-square = 14.17, p = 0.0002; Figure 2B).

Papulopustular lesions. The mean scores for papulopustular lesions were significantly lower in the etanercept group compared to the placebo group at Weeks 1, 3, and 4. This difference disappeared at the third month after the study (Table 2). The probability of being free of papulopustular

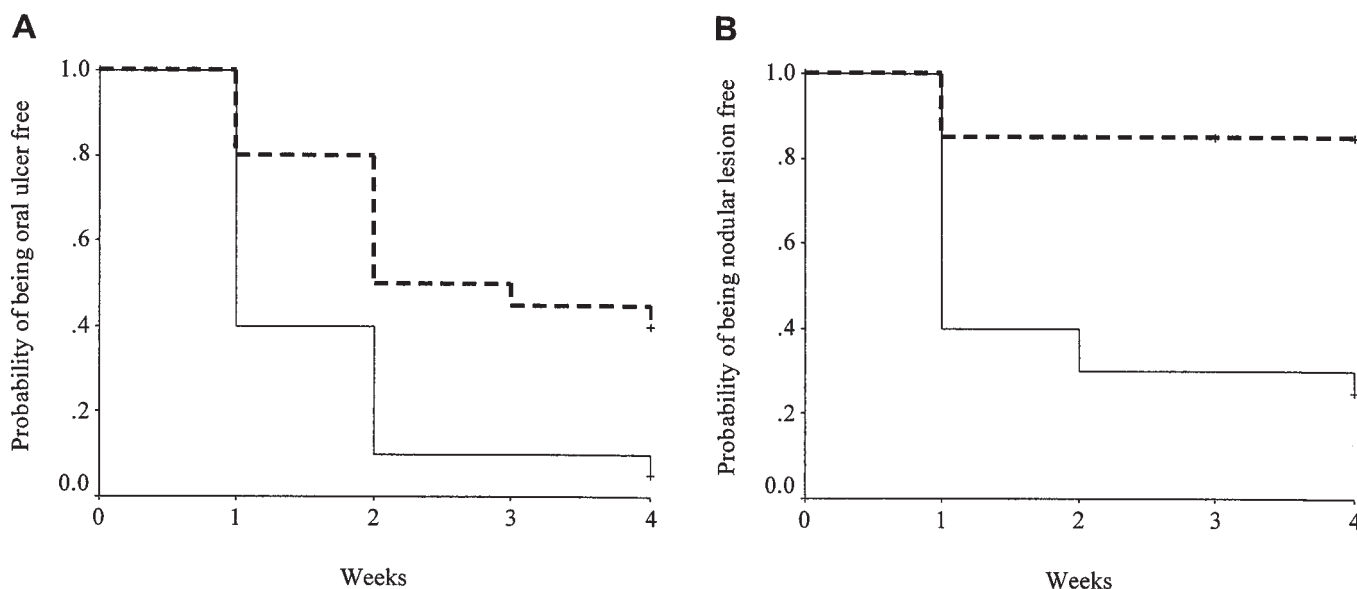


Figure 2. The probability of being (a) oral ulcer-free (chi-square = 9.83, p = 0.0017 log-rank test); and (b) nodular lesion-free (chi-square = 14.17, p = 0.0002 log-rank test) in the etanercept and placebo groups (Kaplan-Maier test). Solid line: etanercept, broken line: placebo.

lesions did not differ between the 2 groups [5% (1/20) in the etanercept group vs 10% (2/20) in the placebo group (log-rank chi-square = 0.63, $p = 0.43$)].

Arthritis. The mean number of swollen joints did not differ between the etanercept and placebo groups at any timepoint (Table 2). The probability of being arthritis-free was 95% (19/20) in the etanercept group, while it was 75% (15/20) in the placebo group (log-rank chi-square = 3.08, $p = 0.081$).

ESR and CRP. The mean ESR (1 hour) and CRP levels were lower in the etanercept group compared to the placebo group at Week 4 [11.8 (95% CI 6.5–17.1) in the etanercept vs 25.1 (95% CI 12.6–37.6) in the placebo group for ESR ($p = 0.03$); and 0.39 mg/dl (95% CI 0.15–0.62) vs 12.06 mg/dl (95% CI –1.17 to 25.29) for CRP ($p = 0.0004$)].

Additional drug use during the study. Two patients (one in the etanercept, one in the placebo arm) continued to use 150 mg/day azathioprine throughout the study because of acute exacerbations of chronic DVT of the legs, and one continued 10 mg/day of prednisolone (in the etanercept arm) due to a painful arthritis. The remaining patients (3 etanercept, 7 placebo) used corticosteroids (topical or systemic), non-steroidal antiinflammatory drugs (NSAID), and paracetamol for varying intervals (Table 3).

A separate analysis was done after excluding the data of the 3 patients who continued to use corticosteroids or azathioprine throughout the study, and censoring the data of the 5 patients who used NSAID or oral corticosteroids sometime during the study. The censoring began at the time these 5 patients started to use these drugs (Weeks 3 and 4 in 3 patients and Week 4 in 2 patients).

In this analysis, the probability of being arthritis-free in the etanercept group reached statistical significance (log-

rank chi-square = 5.33, $p = 0.02$), although there were no differences in the mean number of swollen joints in either group at any time. This change of significance was due to the exclusion of the only patient in the etanercept group who had persistent arthritis throughout the study.

The other change observed in this analysis was the loss of significance in the difference between the mean scores of papulopustular lesions among the 2 groups at Week 4 (Mann-Whitney U: 85, $p = 0.17$). There were no other significant differences in the outcomes related to clinical manifestations and laboratory findings between the 2 groups.

Thirteen patients in the etanercept and 16 in the placebo group received treatment between the end of the study and the evaluation at the third month. Six patients used azathioprine (3 with additional corticosteroids) and 7 patients used colchicine in the etanercept group; while 7 used azathioprine (one with additional corticosteroids), one received α -interferon, and 8 were prescribed colchicine in the placebo group during this interval. Among these 2 groups, there were no differences in the frequency of patients who had to be prescribed a drug for disease control during this time period (chi-square = 1.14, $p = 0.48$). Finally, the only difference between the etanercept and placebo groups at the end of the third month was in the frequency of the mean number of swollen joints, with the etanercept group having more arthritis ($p = 0.04$; Table 2).

Side effects. One patient in the etanercept arm left the trial because of diarrhea at Week 3. He had a normal stool culture and a normal endoscopic examination. He responded well to ornidazole therapy. Another patient in the etanercept arm developed GI involvement manifested by colicky abdominal pain, bloody diarrhea, and an ileocecal ulcer on endoscopy.

Table 3. Additional drugs used during the trial.

Drug	No. of Patients	Etanercept Group			Drug	No. of Patients	Placebo Group		
		Dose	Indication	Duration			Dose	Indication	Duration
Prednisolone	2	50 mg/day, 10 mg/day	GI involvement persistent arthritis	2 weeks (Weeks 3 and 4), throughout the study	Prednisolone	2	30 mg/day, 30 mg/day	Local myositis, vasculitic nodular lesion	2 weeks (Weeks 3 and 4), 2 weeks (Weeks 3 and 4)
Indomethacin	1	75 mg/day	Nodular lesion	1 week (Week 4)	Naproxen	1	550 mg/day	Nodular lesion	1 week (Week 4)
Paracetamol	1	1000 mg/day	Flu	2 weeks (Weeks 3 and 4)	Topical corticosteroids	4		3 for genital ulcers, 1 for oral aphthae	3 weeks (Weeks 1 to 3)
Ornidazole	1*	1 g/day	Infectious colitis	10 days (Weeks 3 and 4)	Azathioprine	1	150 mg/day	DVT	Throughout the study
Azathioprine	1	150 mg/day	DVT	Throughout the study					

DVT: deep vein thrombosis, GI: gastrointestinal. * Dropped out.

His symptoms disappeared with 50 mg/day of prednisolone during the trial, and the remission was sustained with the addition of 150 mg/day azathioprine to a tapered prednisolone dose of 10 mg/day. One patient in the placebo group had elevated liver enzymes (ALT 144 U/l, AST 71 U/l) and a positive hepatitis C virus alongside a negative HCV-RNA, 3 months after the study ended.

No subject reported local erythema or itching at the injection site.

DISCUSSION

This is the first controlled study of a specific anti-TNF- α therapy in BD. Etanercept was beneficial in treating most of the mucocutaneous manifestations at short term. However, it was not effective in suppressing the pathergy and MSU tests.

We were initially interested in the possible effects of etanercept on the pathergy and the MSU reactions and had aimed for a pilot study for these primary endpoints. There were 2 reasons we chose these 2 tests as our primary targets: (1) Pathergy and MSU tests are rather unique to and are indicators of heightened inflammation in BD. Although there is no formal evidence that their positivity correlates well with disease activity or severity^{16,17}, we reasoned that their response to TNF- α blockade would give valuable information concerning the pathogenesis of BD. (2) As the study was not industry-supported (apart from study medications and placebo) the study drug availability was limited. Possible effects on the clinical findings would have been more difficult to discern in a pilot study with a low statistical power, of necessity conducted among a relatively small number of patients. Significant effects at study end, however, were confined to our secondary, clinical endpoints.

Only men were included in this study. BD runs a more severe course in men¹⁸ and with the small number of patients that could be studied we had reasoned that inclusion of women would make the statistical analyses difficult with the inherent better outcome in women.

The observation of a response in the cutaneous manifestations as early as the first week was noteworthy. This has been observed in other inflammatory conditions such as rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis, and was also reported in open trials with another TNF- α blocker, infliximab, for mucocutaneous, ocular, and GI findings in BD⁵⁻¹⁰. The mechanism underlying this rapid response is unknown. Such an early response is uncommon with other immunosuppressives.

During this trial, the clearest effect of etanercept was on oral ulcers and nodular lesions. The absence of a difference between the etanercept and placebo groups in the life table analyses of papulopustular lesions despite significant decreases in the mean score for lesions in the etanercept group was, we believe, due to the lack of total disappearance of these lesions. This is in contrast to observations in nodu-

lar lesions and oral ulcers, where there was not only a decrease in numbers, but total disappearance of lesions in many patients.

The lack of effect on genital ulcerations might indeed be real, or more likely a result of a type II error, both due to the small sample size and the relative infrequency of genital ulcerations during the short study period (a total of 8 ulcers among 3 patients in the etanercept group, and 19 among 5 in the placebo arm).

Similarly, the effect of etanercept on arthritis is not conclusive. As with genital ulcerations, the numbers of events were small in both groups (a cumulative number of 6 swollen joints in one patient in the etanercept group, and 23 among 5 in the placebo arm). Consequently, the data on arthritis are not robust, as exemplified by the change in significance in the life table analysis after the exclusion of a single patient from the etanercept group who continued to use prednisolone throughout the study.

A type II error may also underlie the ineffectiveness of etanercept in suppressing the pathergy and MSU reactions. However, this seems unlikely in view of the rather consistent outcome of the test results. As well, the ineffectiveness of etanercept in suppressing the pathergy reaction does not necessarily imply the lack of importance of TNF- α in the induction of this phenomenon. It may have been due to incomplete neutralization of TNF- α at the dermal level, probably due to the binding properties of etanercept to TNF- α ¹⁹, to a possible increase in the levels of proinflammatory cytokine secretion by T cells after the use of etanercept²⁰, or to the probability of an IL-1 or other proinflammatory cytokine-driven immune response²¹. The same considerations may apply for the ineffectiveness of etanercept in suppressing the MSU test. We do not have information about the immune-histology of this reaction.

One might argue that the differential effects of etanercept on the various manifestations of BD are related to the possibility of differing mechanisms in the pathogenesis of these lesions. This was noted in a study on the effects of thalidomide on BD where the drug was beneficial in suppressing oral aphthae, genital ulcerations, and follicular lesions, whereas it exacerbated nodular lesions²².

All patients (5/5) who had stopped azathioprine before the study were in the placebo group. This raised the possibility of more severe disease among these patients. However, at baseline, the mean frequencies of the clinical manifestations were not different between the placebo and the etanercept groups, and the mean numbers of the mucocutaneous lesions and swollen joints did not differ among patients who stopped azathioprine and the rest of the placebo group at any timepoint (data not shown). Further, azathioprine had to be restarted after the study was over in only 2 of the 5 patients who had stopped it during the washout period before study entry.

In interpreting our results, another issue is the use of

additional drugs during the trial. As noted in Results, there were no significant differences in the additional drugs used between the 2 groups, and our findings remained robust in analyses excluding these patients.

Further, 6 patients in the etanercept and 7 in the placebo arm were prescribed azathioprine after the trial, compared to the 5 patients in the placebo group who used the drug before the trial. This more liberal prescription of azathioprine compared to the pretrial period was probably related to closer followup of these patients due to their participation in a formal study.

It was interesting that patients in the control group had better mean scores for 4 out of 5 clinical variables, with statistical significance in the case of arthritis. It may be said that this was due to a rebound phenomenon in the etanercept group. This is difficult to judge in a post-hoc analysis and we are unaware of reported rebound phenomena with TNF- α blockers in other disease states.

The abrupt decrease in the rate of positivity of the pathergy test in both study arms at Week 1 compared to Week 0 was probably due to the inclusion criteria that required a positive pathergy for every patient. The limited reproducibility of the test is another point to consider.

There was a significant decrease in the MSU-induced erythema in the placebo arm at Week 1 compared to the etanercept arm. We have no explanation for this and interpret it as due to chance. The decrease in the MSU-induced erythema in both study arms at the third month after the study compared to study entry was probably due to a different batch of MSU crystals used at the end of the third month and to the limited reproducibility of the test.

It is known that etanercept injections frequently cause an erythema at the injection site²³, a side effect that we did not observe in this study. This might be due to the small number of patients who received etanercept in this trial or it might be a true biological phenomenon peculiar to BD that needs to be carefully evaluated in future trials.

The development of a noninfectious inflammatory GI involvement in one patient receiving etanercept was noteworthy. Diarrhea responsive to ornidazole in another patient, even though the stool culture was negative, also raised the possibility of an infection triggered by etanercept. Further experience with etanercept will indicate whether these episodes of diarrhea were indeed drug-related.

The mucocutaneous manifestations of BD can, in the majority of patients, be managed more economically by conventional drugs without resorting to relatively expensive anti-TNF therapy. On the other hand, the same skin mucosa manifestations may cause significant morbidity, and may lead to life-threatening pharyngeal stenosis in the occasional patient²⁴.

The beneficial effects observed also suggest a promising role for this drug for more serious manifestations of BD such as arterial, neurological, and eye disease. The optimal

duration of therapy and the possibility of different responses to different TNF- α blockers are other issues that need to be explored in future randomized studies conducted on larger numbers of patients with appropriate power considerations.

ACKNOWLEDGMENT

We thank David MacPeck, MD, Director — Musculoskeletal, Wyeth Pharmaceutical, for his critical review of the manuscript.

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