

ORIGINAL ARTICLE

Etanercept plus Standard Therapy for Wegener's Granulomatosis

The Wegener's Granulomatosis Etanercept Trial (WGET) Research Group*

ABSTRACT

BACKGROUND

The majority of patients with Wegener's granulomatosis have disease flares after conventional medications are tapered. There is no consistently safe, effective treatment for the maintenance of remission.

METHODS

We conducted a randomized, placebo-controlled trial at eight centers to evaluate etanercept for the maintenance of remission in 180 patients with Wegener's granulomatosis. The primary outcome was sustained remission, defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis of 0 for at least six months (scores can range from 0 to 67, with higher scores indicating more active disease). In addition to etanercept or placebo, patients received standard therapy (glucocorticoids plus cyclophosphamide or methotrexate). After remission, standard medications were tapered according to the protocol.

RESULTS

The mean follow-up for the overall cohort was 27 months. Of the 174 patients who could be evaluated, 126 (72.4 percent) had a sustained remission, but only 86 (49.4 percent) remained in remission for the remainder of the trial. There were no significant differences between the etanercept and control groups in the rates of sustained remission (69.7 percent vs. 75.3 percent, $P=0.39$), sustained periods of low-level disease activity (86.5 percent vs. 90.6 percent, $P=0.32$), or the time required to achieve those measures. Disease flares were common in both groups, with 118 flares in the etanercept group (23 severe and 95 limited) and 134 in the control group (25 severe and 109 limited). There was no significant difference between the etanercept and control groups in the relative risk of disease flares per 100 person-years of follow-up (0.89, $P=0.54$). During the study, 56.2 percent of patients in the etanercept group and 57.1 percent of those in the control group had at least one severe or life-threatening adverse event or died ($P=0.90$). Solid cancers developed in six patients in the etanercept group, as compared with none in the control group ($P=0.01$).

CONCLUSIONS

Etanercept is not effective for the maintenance of remission in patients with Wegener's granulomatosis. Durable remissions were achieved in only a minority of the patients, and there was a high rate of treatment-related complications.

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As chairman of the WGET Research Group, Dr. John H. Stone accepts full responsibility for the integrity of the article.

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WEGENER'S GRANULOMATOSIS IS A multisystem inflammatory illness that most often affects the respiratory tract and the kidneys.¹ The introduction of treatment regimens featuring cyclophosphamide and glucocorticoids transformed Wegener's granulomatosis into a disease for which most patients have a remission.² Between 60 percent and 80 percent of patients eventually have disease flares, however, and treatment-induced side effects are a major source of morbidity and mortality.^{1,2} There is no consistently safe, effective therapeutic regimen for the maintenance of remission.

Antibody against tumor necrosis factor α (TNF- α) plays a critical therapeutic role in a variety of inflammatory conditions.³⁻⁸ Several lines of evidence suggest that TNF- α may be an important mediator of Wegener's granulomatosis. In animal models, inhibition of TNF- α markedly decreases the formation of granulomas.⁹ CD4+ T cells from patients with Wegener's granulomatosis produce elevated levels of TNF- α .¹⁰ Serum levels of TNF- α receptor correlate with disease activity.¹¹ TNF- α -positive cells infiltrate renal lesions.¹² In vitro, TNF- α priming of activated neutrophils markedly enhances the ability of antineutrophil cytoplasmic antibodies (ANCA) to stimulate the degranulation of neutrophils.¹³ In uncontrolled studies, treatment with TNF- α inhibitors significantly decreased disease-activity scores in patients with Wegener's granulomatosis.¹⁴⁻¹⁷ To define further the role of TNF- α inhibition in the treatment of this disease, we conducted a multicenter, randomized, double-blind, placebo-controlled trial of etanercept for the maintenance of disease remissions.

METHODS

The protocol for the Wegener's Granulomatosis Etanercept Trial (WGET) was approved by the institutional review board at each center. Details of the design have been published previously.¹⁸ All patients provided written informed consent.

ELIGIBILITY

Patients with a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG)¹⁹ of at least 3 were eligible for the study. Severe Wegener's granulomatosis was defined as disease that posed an immediate threat to either the patient's life or vital organ function. Typical manifestations of severe

disease were rapidly progressive glomerulonephritis, alveolar hemorrhage, and vasculitic neuropathy. Limited disease — for example, sinus, skin, joint, or mild renal manifestations — did not pose such threats at the time of randomization. All patients enrolled met at least two of the five modified criteria of the American College of Rheumatology for the classification of Wegener's granulomatosis.^{18,20} Patients with newly diagnosed disease and those with flares of previously quiescent (existing) disease were eligible.

RANDOMIZATION

Randomization was stratified according to the severity of disease (limited vs. severe) and the center. Standard therapies were assigned on the basis of disease severity.¹⁸

DISEASE-ASSESSMENT INSTRUMENTS

Disease activity was measured by means of the BVAS/WG. Scores can range from 0 to 67, with higher scores indicating more active disease. At each visit, disease activity was also evaluated through global assessments by physicians and patients, for which scores could range from 0 (best) to 10 (worst). The extent of organ damage related to vasculitis was assessed by means of the Vasculitis Damage Index.²¹ Scores for this index can range from 0 to 64, with higher scores indicating more severe damage. The quality of life was assessed with the use of the Medical Outcomes Study 36-Item Short Form General Health Survey (SF-36), which assesses eight aspects of health status: general and mental health, physical and social functioning, physical and emotional role, pain, and vitality.²² Scores on each scale can range from 0 (worst) to 100 (best).

EXPERIMENTAL MEDICATION

After randomization, 25 mg of etanercept twice weekly by subcutaneous injection or placebo was added to standard therapies for Wegener's granulomatosis. Etanercept (Enbrel, Amgen), a soluble TNF- α inhibitor, consists of two extracellular p75 TNF- α -receptor domains linked to the Fc portion of human IgG1. Etanercept was supplied by Amgen for the study. Amgen had no other role in the study design, performance, or reporting.

STANDARD MEDICATIONS

Patients with severe disease received cyclophosphamide and glucocorticoids at enrollment. Those with

limited disease received methotrexate and glucocorticoids. Once the disease was controlled, the doses of the standard medications were tapered according to the protocol. The starting daily dose of prednisone ranged from 0.5 to 1.0 mg per kilogram of body weight. At the investigators' discretion, patients with severe Wegener's granulomatosis could receive 1 g of methylprednisolone per day three times before starting prednisone. Patients with limited disease initially received 0.25 mg of methotrexate per kilogram per week, and the dose was increased to a maximum of 25 mg per week.¹⁸ Patients with severe disease received 2 mg of cyclophosphamide per kilogram per day (the dose was lowered in the event of renal dysfunction).¹⁸

The prednisone-tapering protocol led to the discontinuation of prednisone within six months after randomization, assuming that no relapse occurred.¹⁸ After three to six months of cyclophosphamide, patients in remission discontinued cyclophosphamide and began methotrexate. Methotrexate was continued for 12 months after the achievement of remission, whereupon the dose was decreased by 2.5 mg per month. Patients in remission whose serum creatinine levels exceeded 2.0 mg per deciliter (176.8 μ mol per liter) received 2 mg of azathioprine per kilogram per day. After 12 months of remission, the dose of azathioprine was decreased by 25 mg per month.

TREATMENT OF DISEASE FLARES

Severe flares were treated with cyclophosphamide and glucocorticoids. Limited flares were treated with increases in the dose of methotrexate, prednisone, or both.¹⁸ After four weeks at the increased dose of prednisone, the tapering regimen was resumed.

CONCOMITANT MEDICATIONS

All patients received prophylaxis against pneumocystis infection and osteoporosis.¹⁸

DATA COLLECTION

Follow-up evaluations occurred at 6 and 12 weeks, then every 3 months. Patients were followed until 12 months after the randomization of the last patient.¹⁸

OUTCOMES

The primary outcome measure was sustained disease remission, defined as a BVAS/WG of 0 for at

least six months. All patients who died were included in the primary analysis. Surviving patients who had less than nine months of follow-up data were not included in analyses of sustained remission. Secondary outcome measures included the number and rate of flares during the treatment phase, the percentage of patients with a sustained low level of disease activity (defined by a BVAS/WG of less than 3 for at least six months), the percentage of patients with a remission (defined by a BVAS/WG of 0), the cumulative area under the curve (AUC) for the

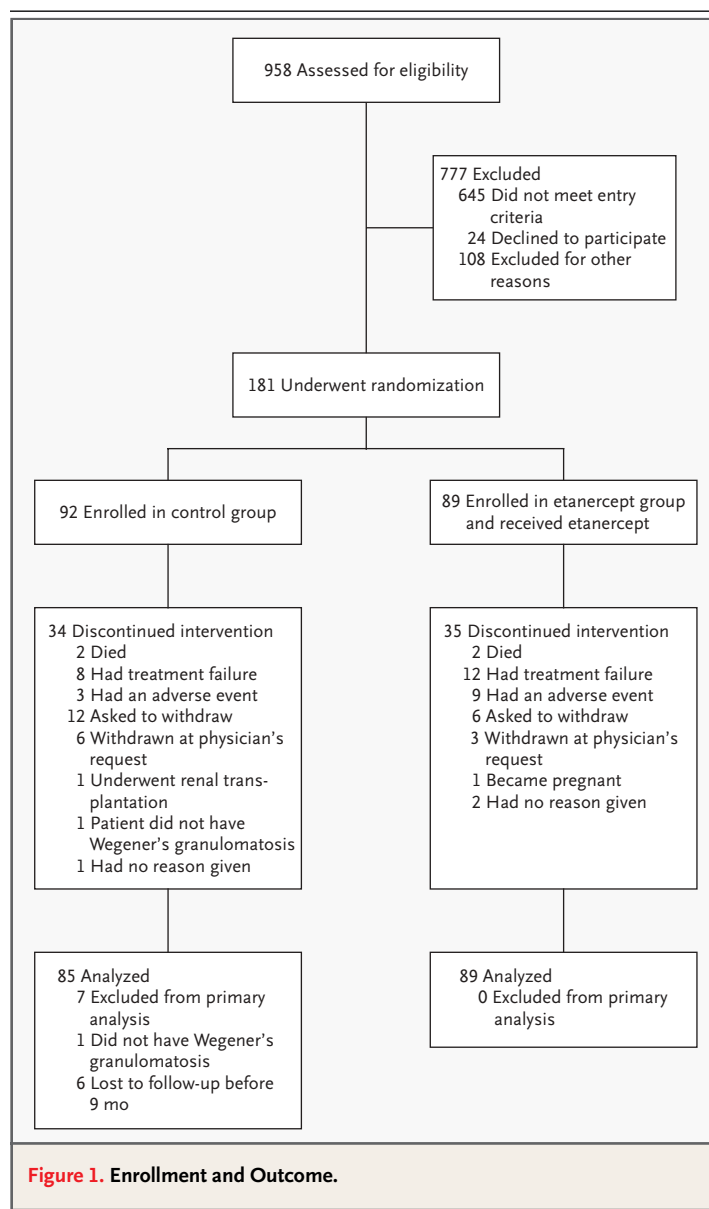


Figure 1. Enrollment and Outcome.

Table 1. Baseline Characteristics.*

Characteristic	Etanercept Group (N=89)	Control Group (N=91)	P Value†
Age at onset of symptoms (yr)	52.4±13.9	47.5±16.5	0.01
Sex (%)			0.43
Male	62.9	57.1	
Female	37.1	42.9	
Race or ethnic group (%)			0.78
White, non-Hispanic	91.0	93.4	
Black, non-Hispanic	2.3	1.1	
Hispanic	4.5	3.3	
Other	2.2	2.2	
Limited disease (%)	30.3	27.5	0.67
Disease newly diagnosed at enrollment (%)	34.8	53.9	0.01
Time since onset of symptoms (mo)			
New diagnosis			0.57
Median	5.1	4.0	
Interquartile range	3.2–10.1	2.5–9.7	
Previous diagnosis			0.31
Median	48	40	
Interquartile range	25–81	20–75	
Time since diagnosis (mo)			
New diagnosis			0.57
Median	0.79	0.66	
Interquartile range	0.36–1.38	0.36–1.12	
Previous diagnosis			0.13
Median	36	25	
Interquartile range	19–61	10–50	
Disease-assessment indexes‡			
BVAS/WG	6.5±3.0	7.5±3.7	0.06
Physicians' global assessment	5.3±2.3	5.8±2.3	0.10
Patients' global assessment	6.5±2.8	6.4±2.7	0.68
Vasculitis Damage Index	1.6±1.9	1.0±1.4	0.09
SF-36			
Physical score	34.4±9.7	32.6±9.6	0.16
Mental score	45.4±12.2	42.9±10.9	0.11

BVAS/WG, adverse events related to Wegener's granulomatosis or its treatment, and the quality of life. Disease flares were defined by an increase of at least one point in the BVAS/WG.

STATISTICAL ANALYSIS

Given the enrollment of 180 patients, the study had the statistical power to detect absolute differences

between groups in the rate of remission ranging from 15 to 22 percent, depending on the percentage of patients in the control group who had sustained remissions.¹⁸ Primary analyses were performed on an intention-to-treat basis. We performed unadjusted analyses and analyses adjusted for such factors as disease severity, presence or absence of newly diagnosed disease at enrollment, baseline renal func-

Table 1. (Continued.)			
Characteristic	Etanercept Group (N=89)	Control Group (N=91)	P Value†
Organ involvement (%)			
Systemic‡	65.2	78.0	0.06
Skin	15.7	24.2	0.16
Mucous membranes or eyes	24.7	27.5	0.67
Ear, nose, and throat	69.7	83.5	0.03
Cardiovascular system	0	2.2	0.50
Gastrointestinal tract	0	2.2	0.50
Pulmonary system	51.7	68.1	0.02
Renal system	52.8	55.0	0.77
Nervous system	6.7	12.1	0.22
Other	44.9	35.2	0.18
Laboratory results¶			
Mean serum creatinine (mg/dl)	1.85±2.05	1.62±1.76	0.36
ANCA			
Ever positive by IF (%)	85.4	89.0	0.47
C-ANCA (% of total ANCA positive by IF)	85.3	89.7	
P-ANCA (% of total ANCA positive by IF)	14.7	10.3	
ANCA ever positive by EIA (%)			
Positive for PR3-ANCA	70.8	74.7	0.09
Positive for MPO-ANCA	16.9	6.6	0.03

* Plus-minus values are means ±SD. To convert values for creatinine to micromoles per liter, multiply by 88.4. Race or ethnic group was self-reported.

† The chi-square or Fisher's exact test was used for categorical data; Wilcoxon's rank-sum test was used for continuous data.

‡ The criteria of the American College of Rheumatology were used to classify Wegener's granulomatosis. Scores for the BVAS/WG for newly diagnosed disease or flares can range from 0 to 67, with higher scores indicating more active disease. A score of 0 indicates remission. Global assessment scores can range from 0 (best) to 10 (worst). Scores for the Vasculitis Damage Index can range from 0 to 64, with higher scores indicating greater degrees of damage. Scores for each aspect of the SF-36 can range from 0 (worse) to 100 (best). A score of 50 represents the mean score for the healthy U.S. population.

§ This category refers to systemic signs or symptoms of disease activity — specifically, arthritis, arthralgias, or fever (temperature ≥38.0°C).

¶ ANCA denotes antineutrophil cytoplasmic antibodies, IF immunofluorescence, C-ANCA cytoplasmic ANCA, P-ANCA perinuclear ANCA (detected by an immunofluorescence assay), EIA enzyme immunoassay, and PR3-ANCA and MPO-ANCA ANCA directed against proteinase 3 and myeloperoxidase, respectively (detected by EIA).

tion, and the BVAS/WG at entry. Adjustment variables were selected on the basis of their potential associations with treatment assignment and trial outcomes.²³

We used Cox proportional-hazards models to identify differences in mortality and other time-to-event outcomes.²⁴ The effects of treatment on flare rates and adverse events were examined with the use of Poisson models.²⁵ Generalized estimating equations were used to assess repeated measures of change for continuous outcomes.²⁶ AUC analyses

of the BVAS/WG were performed after logarithmic transformation of the scores. The AUC was calculated as the mean BVAS/WG for sequential visits, multiplied by the time between visits and summed for all visits for a given patient.

Adverse events, defined as any untoward medical occurrences in patients who received etanercept, regardless of their presumed relationships to treatment, were graded according to the National Cancer Institute Toxicity Grading Scale.²⁷ Using the Surveillance, Epidemiology, and End Results (SEER)

database,²⁸ we calculated a standardized incidence ratio (defined as the number of observed cases divided by the number of expected cases and multiplied by 100) for the cancers observed.

RESULTS

ENROLLMENT AND RANDOMIZATION

Between June 9, 2000, and September 30, 2002, we screened 958 patients with a diagnosis of Wegener's granulomatosis and enrolled 181 of them (Fig. 1). Eighty-nine patients (49.4 percent) were randomly assigned to receive etanercept and 92 (50.6 percent) to receive placebo. One patient in the control group was removed from the trial six weeks after randomization because the diagnosis of Wegener's granulomatosis was discovered to be incorrect.²⁹ The median duration of treatment was 25 months for etanercept and 19 months for placebo ($P=0.50$). Fifty-four of the 89 patients in the etanercept group (60.7 percent) completed the study regimen, as

compared with 58 of the 91 patients in the control group (63.0 percent). The reasons for discontinuation of the assigned treatments are given in Figure 1. The mean duration of follow-up was 27 months in the overall cohort. A total of 174 patients (96.7 percent) had sufficient follow-up to be evaluated for the primary outcome. Six patients, all of whom were in the control group, were lost to follow-up before nine months.

BASELINE CHARACTERISTICS

The patients' baseline characteristics are shown in Table 1. A full description of the baseline disease characteristics of the WGET cohort has been published.²⁹ The mean age at entry was 49.8 years (52.4 years in the etanercept group and 47.5 years in the control group, $P=0.03$). There were 108 men (60.0 percent) and 72 women (40.0 percent). The majority (92.2 percent) were white.

Among the 180 patients, 128 (71.1 percent) had severe disease and 52 (28.9 percent) had limited disease. The mean (\pm SD) BVAS/WG at entry was 6.5 ± 3.0 in the etanercept group and 7.5 ± 3.7 in the control group ($P=0.06$). Eighty patients (44.4 percent) had newly diagnosed Wegener's granulomatosis. Fewer patients in the etanercept group than in the control group had newly diagnosed Wegener's granulomatosis at enrollment (34.8 percent vs. 53.9 percent, $P=0.01$), but the rate of previous exposures to cyclophosphamide, methotrexate, and azathioprine did not differ significantly between groups (data not shown).

PRIMARY OUTCOME MEASURE

Sixty-two of 89 patients in the etanercept group had a sustained remission (one lasting at least six months), as compared with 64 of 85 patients in the control group (69.7 percent vs. 75.3 percent, $P=0.39$) (Fig. 2). There was no significant difference between groups in the time to the achievement of a sustained remission. Although more patients in the etanercept group than in the control group had a history of failed treatment before enrollment (58 vs. 39), the percentages of such patients who did not have a sustained remission were approximately equal in the two groups (32.8 percent [19 patients] and 33.3 percent [13 patients], respectively). There was no significant interaction between having a history of more than one disease flare before entry and treatment assignment ($P=0.87$).

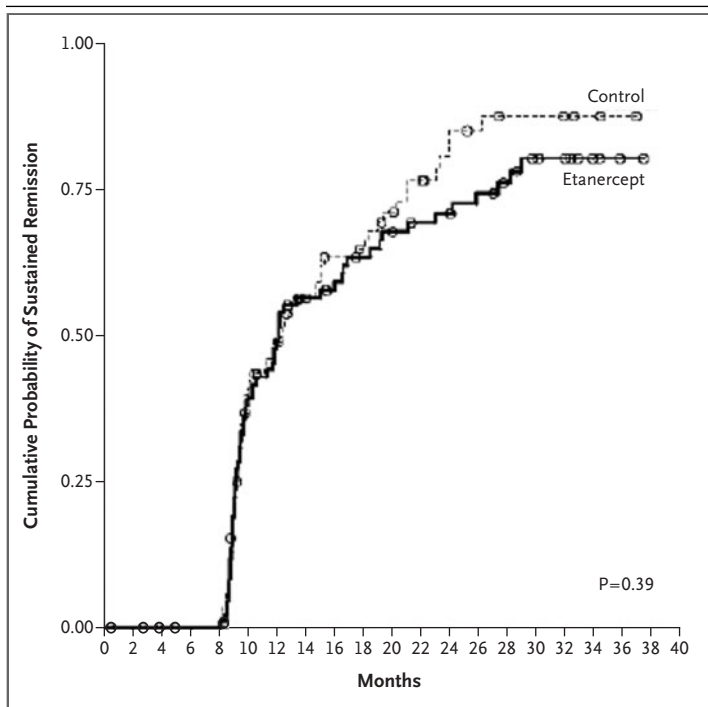


Figure 2. Kaplan–Meier Estimates of the Time to Sustained Remission.

Sustained remission was defined as a BVAS/WG of 0 for a minimum of six months. The P value was determined by means of the log-rank test. Circles indicate censored observations.

Table 2. Sustained Remission, Achievement of Remission, Disease Control, and Disease Flares.*

Variable	Control Group	Etanercept Group	Hazard Ratio (95% CI)†	P Value
	<i>no./total no. (%)</i>			
Sustained remission				
BVAS/WG=0 for ≥6 mo	64/85 (75.3)	62/89 (69.7)	0.86 (0.60–1.22)	0.39
Analyses stratified according to disease severity at baseline				
Severe	47/60 (78.3)	44/62 (71.0)	0.91 (0.60–1.37)	0.85‡
Limited	17/25 (68.0)	18/27 (66.7)	0.82 (0.42–1.60)	
Analyses stratified according to new or existing disease at baseline				
New disease	38/46 (82.6)	23/31 (74.2)	0.82 (0.49–1.38)	0.35‡
Existing disease	26/39 (66.7)	39/58 (67.2)	1.07 (0.65–1.76)	
Remission				
BVAS/WG=0 at any time during trial	84/91 (92.3)	80/89 (89.9)	0.86 (0.63–1.18)	0.35
Analyses stratified according to disease severity at baseline				
Severe	61/66 (92.4)	57/62 (91.9)	0.91 (0.63–1.32)	0.77‡
Limited	23/25 (92.0)	23/27 (85.2)	0.80 (0.44–1.43)	
Analyses stratified according to new or existing disease at baseline				
New disease	46/49 (93.9)	28/31 (90.3)	0.71 (0.44–1.16)	0.31‡
Existing disease	38/42 (90.5)	52/58 (89.7)	1.03 (0.67–1.57)	
Sustained low level of disease activity				
BVAS/WG <3 for ≥6 mo	77/85 (90.6)	77/89 (86.5)	0.85 (0.62–1.17)	0.32
Analyses stratified according to disease severity at baseline				
Severe	57/60 (95.0)	52/62 (83.9)	0.70 (0.48–1.03)	0.11‡
Limited	20/25 (80.0)	25/27 (92.6)	1.24 (0.69–2.24)	
Analyses stratified according to new or existing disease at baseline				
New disease	44/46 (95.7)	28/31 (90.3)	0.74 (0.46–1.21)	0.26‡
Existing disease	33/39 (84.6)	49/58 (84.5)	1.09 (0.70–1.70)	
<i>no. of flares/total no. of patients (no./100 person-yr)</i>				
Disease flares during study treatment				
All flares	116/91 (74.1)	107/88 (66.3)	0.89 (0.62–1.28)	0.54
Adjustment for existing disease			0.78 (0.55–1.11)	0.17
Severe flares	20/91 (12.8)	27/88 (14.9)	1.05 (0.61–1.80)	0.87

* Values are the number of events over the total number of patients who were followed at least to the scheduled 9-month visit (visit window, 7.5 to 10.5 months) or who died before this visit (data were censored at the time of death) for the analysis of sustained remission or sustained low-level disease activity or the total number of patients who had at least one follow-up visit for the analysis of disease flares. The BVAS/WG can range from 0 to 67, with higher scores indicating more active disease. A BVAS/WG of 0 indicates remission. CI denotes confidence interval.

† Hazard ratios were obtained by means of a Cox proportional-hazards model for time-to-event analysis for sustained remission, remission, and disease control.

‡ The P value is for the interaction between treatment assignment and disease stratum. Relative risk is shown in which a Poisson regression model was used for the analysis of rate of disease flares.

SECONDARY OUTCOME MEASURES*Numbers of Flares and Flare Rates*

The numbers of flares and the flare rates are shown in Table 2, along with other secondary outcome measures. Only 38 patients in the etanercept group (42.7 percent) and 39 patients in the control group (42.9 percent) had no disease flares during the trial. Disease flares were common in both groups, with a total of 118 flares in the etanercept group (23 severe and 95 limited) and 134 in the control group (25 severe and 109 limited). Among the 62 patients who had a sustained remission in the etanercept group, 19 (30.6 percent) later relapsed. In comparison, 21 of the 64 patients who had a sustained remission in the control group (32.8 percent) later relapsed. Overall, only 86 of 174 patients (49.4 percent) who completed the trial had a sustained remission that was maintained for the remainder of the trial. The rates of disease flares during treatment did not differ significantly between the etanercept and control groups (66.3 per 100 person-years and 74.1 per 100 person-years, respectively; relative risk of a disease flare, 0.89; 95 percent confidence interval, 0.62 to 1.28; $P=0.54$). The AUC for BVAS/WG also did not differ significantly between the etanercept group and the control group: 6.0 ± 1.0 per day and 6.0 ± 0.8 per day, respectively.

Vasculitis Damage Index

The mean score for the Vasculitis Damage Index increased from 1.6 at baseline to 2.0 at the end of the trial in the etanercept group and from 1.0 to 1.7 in the control group ($P=0.50$). The most frequently listed items in the overall cohort were hearing loss in 25.6 percent and proteinuria (more than 0.5 g of protein per 24 hours) in 18.9 percent.

Quality of Life

The quality of life improved in both groups during the trial. Scores for the physical and mental health aspects of the SF-36 improved by 7.7 and 5.7 points, respectively, in the etanercept group and by 8.4 and 8.0 points, respectively, in the control group.

ADVERSE EVENTS

The numbers of severe events (grade 3), life-threatening events (grade 4), and deaths (grade 5) were approximately equal in the two groups; 56.2 percent of patients in the etanercept group and 57.1 percent of those in the control group had at least one adverse event of grade 3, 4, or 5 ($P=0.90$). (Many

patients had more than one grade 3 or 4 adverse event.) The adverse events included six deaths, four in the etanercept group (cholangiocarcinoma in one, sepsis in one, and cardiac arrest in two) and two in the control group (cardiac arrest in one and sepsis in one).

Cytopenias, Infections, Congestive Heart Failure, and Venous Thrombotic Events

The incidence of cytopenias, infections, congestive heart failure, or venous thrombotic events was similar in the two groups. For example, 49.4 percent of patients in each group had infections that ranged in severity from moderate to fatal (grades 2 through 5) ($P=0.99$). Nineteen patients in the trial had a total of 20 venous thrombotic events (deep venous thromboses, pulmonary emboli, or both),³⁰ 10 events in each group ($P=0.92$).

Cancer

All six solid cancers identified during the trial occurred in the etanercept group ($P=0.01$). These cancers included two cases of mucinous adenocarcinoma of the colon, one metastatic cholangiocarcinoma, one renal-cell carcinoma, one breast carcinoma, and one liposarcoma (a recurrence after a primary resection 10 years before enrollment). There was no significant difference in the occurrence of cutaneous basal-cell or squamous-cell carcinomas, with three cases in the etanercept group and four in the control group.

We compared the six solid cancers in the etanercept group against the SEER database,²⁸ which includes all invasive cancers plus urinary-bladder cancer and breast carcinoma in situ. On the basis of age- and sex-specific incidences rates, 1.92 solid cancers were expected in the etanercept group (standardized incidence ratio, 312 percent; $P=0.004$). During the six-month follow-up period after study treatment, three additional solid cancers were diagnosed. One patient in the etanercept group had an adenocarcinoma of the prostate, and one patient in the control group had a cholangiocarcinoma. There was also one metastatic renal-cell carcinoma in a patient who had originally been assigned to the placebo group but who had discontinued treatment after a second severe disease flare. For 14 months before the renal-cell carcinoma was diagnosed, he had received infliximab (Remicade, Centocor), a monoclonal antibody inhibitor of TNF- α .

DISCUSSION

We found no significant differences between the etanercept and control groups in rates of sustained remissions, sustained periods of low levels of disease activity, time to sustained remission, AUC for BVAS/WG, or numbers of disease flares. Our findings do not provide support for the use of etanercept in either the induction or the maintenance of remission in patients with Wegener's granulomatosis. Our results underscore three points: standard therapy fails to induce durable remissions in the majority of patients, etanercept does not enhance the effects of standard therapy, and even with the shorter courses of cyclophosphamide now regarded as the standard of care, adverse events are common and frequently severe, with or without the addition of specific TNF- α blockade.

Our results contrast with data from the Cyclophosphamide versus Azathioprine as Remission Maintenance Therapy for ANCA-Associated Vasculitis (CYCAZAREM) Study,³¹ a randomized comparison of cyclophosphamide with azathioprine for the maintenance of remission in ANCA-associated vasculitis. The CYCAZAREM Study found that 7 percent of patients had a severe relapse and 15 percent had a relapse of any severity, as compared with the respective rates of 22 percent and 57 percent in WGET. There are several explanations for the reported differences between these two trials.

In the CYCAZAREM Study, 39 percent of the patients had microscopic polyangiitis, a form of ANCA-associated vasculitis that is less likely to relapse than is Wegener's granulomatosis. Furthermore, in order to qualify as a disease flare, there had to be at least three minor manifestations of active disease, whereas WGET required only one. It is therefore conceivable that episodes of minor disease activity were undercounted in the CYCAZAREM Study. The longer follow-up in our trial (27 months, vs. 18 months in CYCAZAREM) may also have led to a higher percentage of observed disease flares. Perhaps most important, however, patients in the CYCAZAREM Study continued to receive 7.5 mg of prednisolone per day after the achievement of remission. In contrast, the WGET protocol called for the cessation of glucocorticoid therapy after six months.

Given the efficacy of etanercept for several other rheumatologic diseases³⁻⁸ and the rationale for the use of TNF- α inhibition in Wegener's granuloma-

tosis, the negative results of our trial are noteworthy. There are several potential explanations. First, the dose of etanercept may not have been sufficient to achieve a therapeutic effect. The results of most studies using higher doses, however (e.g., those involving patients with rheumatoid arthritis or congestive heart failure), have not supported the use of more than 25 mg of etanercept twice weekly. A phase 3 trial of patients with rheumatoid arthritis (Amgen protocol 016.0025, available from the manufacturer) showed similar rates of response according to the criteria of the American College of Rheumatology in the group given 25 mg and the group given 50 mg, but a trend toward more adverse effects with the 50-mg dose. The negative results of our trial diminish any enthusiasm for studying higher doses of etanercept in the treatment of Wegener's granulomatosis.

Second, despite the importance of TNF- α in granuloma formation,⁹ etanercept could be ineffective in diseases characterized by granulomatous inflammation. The results in WGET, a very large trial of etanercept in a granulomatous disease are consistent with those in smaller studies of etanercept in patients with Crohn's disease and sarcoidosis that have not demonstrated clinical benefits.^{32,33} In addition to the failure of etanercept to affect granulomatous disease, however, it has also been shown to be ineffective in nongranulomatous conditions, such as heart failure and sepsis. Our results emphasize the importance of testing new therapies in rigorous, randomized clinical trials before extrapolating the efficacious results of a therapy for one disease to those for another.

Third, there may be differences in efficacy among the various approaches to the inhibition of TNF- α . In contrast to etanercept, infliximab binds in vitro to lymphocytes and induces apoptosis in activated cells.³⁴ The limited data available on the use of infliximab in Wegener's granulomatosis, however, aroused concern, particularly with respect to the number of disseminated infections and the frequency of relapses during infliximab therapy.¹⁵⁻¹⁷

Our trial results also provide important information about adverse events in the treatment of Wegener's granulomatosis. In the past few years, the shorter courses of cyclophosphamide (three to six months) used in the WGET have become the standard of care,³¹ yet there remain few data about adverse events associated with these shorter regimens. The sobering numbers of adverse events in both

groups in the WGET (more than 50 percent of patients in each group had at least one severe or life-threatening event or died) demonstrate that even with careful monitoring, shorter courses of cyclophosphamide are still associated with substantial morbidity and mortality.

Our finding of six solid tumors in the etanercept group merits further review. All etanercept-treated patients in whom solid tumors developed were also treated with cyclophosphamide during the trial. Moreover, several had received cyclophosphamide for prolonged periods to treat active disease before enrollment. Cyclophosphamide is known to increase the risk of cancer, particularly bladder and hematopoietic cancers. However, there were no significant differences between groups in the numbers of patients with histories of cyclophosphamide use or the duration of use or maximal dose of that agent. It is possible, therefore, that the combination of TNF- α inhibition and cyclophosphamide heightens the risk of cancer beyond that observed with cyclophosphamide alone.

Our study has potential limitations. First, referral bias may have resulted from the tendency of sicker patients to be referred to tertiary care centers. Our patients were quite similar to cohorts with Wegener's granulomatosis at the National Institutes of

Health and in Germany.^{1,2,29} There are no large, population-based cohorts of patients with Wegener's granulomatosis against which to compare the WGET cohort. Second, some adverse events (osteoporosis and azoospermia) were probably underreported because we did not test systematically for all such potential complications.

In conclusion, our results do not support the use of etanercept in regimens designed to either induce or maintain remissions in patients with Wegener's granulomatosis. Although none of our patients died of disseminated disease, a marked contrast to results in earlier eras, only a minority of patients had no disease flares during the trial. Disease remissions were obtained at a high cost of treatment-associated complications. Further investigation of the potential association among TNF- α inhibition, cyclophosphamide, and cancer is appropriate.

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Dr. Davis reports serving on the speakers bureau for Amgen.

APPENDIX

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REFERENCES

- Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener's granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992;116:488-98.
- Reinhold-Keller E, Beuge N, Latza U, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. *Arthritis Rheum* 2000;43:1021-32. [Erratum, *Arthritis Rheum* 2000;43:2379.]
- Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *N Engl J Med* 1997;337:141-7.
- Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000;343:1594-602.
- Davis JC Jr, Van Der Heijde D, Braun J, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003;48:3230-6.
- Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003;349:2014-22.
- Mease DJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. *Lancet* 2000;356:385-90.
- Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;340:1398-405.
- Kindler V, Sappino AP, Grau GE, Piguat PF, Vassalli P. The inducing role of tumor necrosis factor in the development of bacterial granulomas during BCG infection. *Cell* 1989;56:731-40.
- Ludviksson BR, Sneller MC, Chua KS, et al. Active Wegener's granulomatosis is associated with HLA-DR* CD4* T cells exhibiting an unbalanced Th1-type T cell cytokine

- pattern: reversal with IL-10. *J Immunol* 1998; 160:3602-9.
11. Nassonov E, Samsonov M, Tilz GP, et al. Serum concentrations of neopterin, soluble interleukin 2 receptor, and soluble tumor necrosis factor receptor in Wegener's granulomatosis. *J Rheumatol* 1997;24:666-70.
 12. Noronha IL, Kruger C, Andrassy K, Ritz E, Waldherr R. In situ production of TNF-alpha, IL-1 beta and IL-2R in ANCA-positive glomerulonephritis. *Kidney Int* 1993;43:682-92.
 13. Falk RJ, Terrell RS, Charles LA, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies induce neutrophils to degranulate and produce oxygen radicals in vitro. *Proc Natl Acad Sci U S A* 1990;87:4115-9.
 14. Stone JH, Uhlfelder ML, Hellmann DB, Crook S, Bedocs NM, Hoffman GS. Etanercept combined with conventional treatment in Wegener's granulomatosis: a six-month open-label trial to evaluate safety. *Arthritis Rheum* 2001;44:1149-54.
 15. Bartolucci P, Ramanoelina J, Cohen P, et al. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. *Rheumatology (Oxford)* 2002;41:1126-32.
 16. Lamprecht P, Voswinkel J, Lilienthal T, et al. Effectiveness of TNF-alpha blockade with infliximab in refractory Wegener's granulomatosis. *Rheumatology (Oxford)* 2002; 41:1303-7.
 17. Booth AD, Bacon PA, Griffith ME, et al. Infliximab in ANCA-associated vasculitis: the "ACTIVE" trial. *Kidney Blood Press Res* 2003;26:292-3.
 18. The WGET Research Group. Design of the Wegener's Granulomatosis Etanercept Trial (WGET). *Control Clin Trials* 2002;23: 450-68.
 19. Stone JH, Hoffman GS, Merkel PA, et al. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. *Arthritis Rheum* 2001;44:912-20.
 20. Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum* 1990;33: 1101-7.
 21. Exley AR, Bacon PA, Luqmani RA, et al. Development and initial validation of the Vasculitis Damage Index (VDI) for the standardized clinical assessment of damage in the systemic vasculitides. *Arthritis Rheum* 1997;40:371-80.
 22. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care* 1994;32:40-66.
 23. Canner PL. Covariate adjustment of treatment effects in clinical trials. *Control Clin Trials* 1991;12:359-66.
 24. Cox DR. Regression models and lifetables. *J R Stat Soc [B]* 1972;34:187-220.
 25. Breslow NE. Test of hypotheses in an overdispersed Poisson regression and other quasi-likelihood models. *J Am Stat Assoc* 1990;85:565-71.
 26. Zeger S, Liang K. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121-30.
 27. National Cancer Institute. Toxicity grading scale. (Accessed January 3, 2005, at <http://ctep.info.nih.gov>.)
 28. Surveillance, Epidemiology, and End Results (SEER) Program database. (Accessed January 3, 2005, at <http://www.seer.cancer.gov>.)
 29. Stone JH, WGET Research Group. Limited versus severe Wegener's granulomatosis: baseline data from the Wegener's Granulomatosis Etanercept Trial. *Arthritis Rheum* 2003;48:2299-309.
 30. Merkel PA, Lo GH, Holbrook JT, et al. High incidence of venous thrombotic events among patients with Wegener's granulomatosis. *Ann Intern Med* (in press).
 31. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003;349:36-44.
 32. Sandborn WJ, Hanauer SB, Katz S, et al. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2001;121: 1088-94.
 33. Utz JP, Limper AH, Kalra S, et al. Etanercept for the treatment of stage II and III progressive pulmonary sarcoidosis. *Chest* 2003; 124:177-85.
 34. Van den Brande JM, Braat H, van den Brink GR, et al. Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. *Gastroenterology* 2003;124:1774-85.

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