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Etanercept Combined With Conventional Treatment in Wegener's Granulomatosis

A Six-Month Open-Label Trial to Evaluate Safety

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Objective. **To evaluate the safety of etanercept (Enbrel) in patients receiving conventional treatment for Wegener's granulomatosis (WG).**

Methods. **We performed a 6-month open-label trial of etanercept (25 mg subcutaneously twice weekly) which was added to standard therapies for WG (glucocorticoids, methotrexate, cyclophosphamide, azathioprine, cyclosporine) and prescribed according to disease severity. Evaluations of clinical response were determined by the Birmingham Vasculitis Activity Score for WG (BVAS/WG) in 20 patients with persistently active disease or with new flares of previously established WG. Fourteen of the 20 patients (70%) had etanercept added as the only new therapeutic variable.**

Results. **Injection site reactions (ISRs) were the most common adverse event related to etanercept (8 episodes in 5 patients [25%]; <1% of all injections). All ISRs were mild. Two patients had a combined total of 5 hospitalizations (1 patient had 4), but no hospitalizations were attributable solely to etanercept-related adverse events. One patient with severe subglottic stenosis developed pneumococcal tracheobronchitis and subsequently had a localized *Herpes zoster* infection. Nineteen patients (95%) were still taking etanercept at 6 months, the single exception being a patient who developed progression of orbital (retro-bulbar) disease at 4 months. There were no deaths. The mean BVAS/WG at entry was 3.6 (range 1–8), which decreased at 6 months to 0.6 ($P < 0.001$, 95% confidence interval [95% CI] −4.0 to −2.1). Among the 14 patients in whom etanercept was the only new treatment variable, the mean daily prednisone dose decreased from 12.9 mg at entry to 6.4 mg at 6 months. This comparison did not achieve statistical significance (difference −6.5; $P = 0.19$, 95% CI −16.6 to +3.6). Sixteen of the patients (80%) achieved BVAS/WG scores of 0 at some point. However, intermittently active disease was observed in 15 patients (75%).**

Conclusion. **In this open-label trial, etanercept used in combination with standard treatments was well-tolerated in patients with WG. Adverse events were few. BVAS/WG scores improved at 6 months, but intermittently active WG (occasionally severe) was common. A randomized, double-masked trial to assess the efficacy of etanercept in WG has begun.**

Wegener's granulomatosis (WG) is characterized by a multifocal inflammatory illness that most often affects the upper and lower respiratory tracts and the kidneys (1). Conventional treatment regimens induce remissions in the majority of patients, but disease relapses are a common problem with regimens using either cyclophosphamide (CYC) or methotrexate (MTX) (1–3). Thus, a major current limitation in the treatment of WG is the absence of a safe, well-tolerated means of maintaining disease remissions.

Etanercept (Enbrel; Immunex Corporation, Seattle, WA), a fusion protein consisting of 2 recombinant p75 tumor necrosis factor (TNF) receptors linked to the

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Fc portion of human IgG1, is a powerful antagonist of TNF (4). Specific TNF inhibition is effective in several forms of inflammatory arthritis, including rheumatoid arthritis (5,6). Evidence suggests that abnormal regulation of TNF may also play a major role in WG. In animal models, granuloma formation is markedly impaired by antibodies directed against TNF (7). Transcription of the TNF gene is enhanced in peripheral blood mononuclear cells from patients with WG (8). CD4+ T cells from patients with WG produce elevated levels of TNF (9). Serum levels of soluble receptors for TNF are elevated in patients with active WG, and normalize with the induction of remission (10). Studies of renal biopsy tissue by immunohistochemistry, polymerase chain reaction, and in situ hybridization from patients with pauci-immune glomerulonephritis confirm that TNF-positive cells infiltrate histologically active renal lesions (11). In vitro priming of activated neutrophils with TNF markedly enhances the ability of antineutrophil cytoplasmic antibodies (ANCA) to stimulate neutrophil degranulation, potentially fueling the vasculitis associated with this disorder (12).

Because there is no published experience with the use of etanercept in WG, we designed a study to evaluate the safety of this agent used in conjunction with conventional treatments. Twenty patients with unequivocal WG who were experiencing flares or persistence of active disease were enrolled in an open-label trial.

PATIENTS AND METHODS

Patient recruitment. This study was approved by the Johns Hopkins University (JHU) Joint Committee on Clinical Investigation and the Institutional Review Board of the Cleveland Clinic Foundation (CCF). All patients provided informed consent. Patients were recruited from the vasculitis centers of both institutions (9 from JHU, 11 from CCF). There were 3 inclusion criteria for this trial: 1) a clinical diagnosis of WG after the exclusion of infections, malignancies, systemic autoimmune disorders, and other forms of vasculitis; 2) a minimum Birmingham Vasculitis Activity Score for WG (BVAS/WG) of 1 (13); and 3) a history of at least 2 of the 5 modified 1990 American College of Rheumatology (ACR) criteria for the classification of WG (14). The modification of the ACR criteria consisted of the addition of antibodies to proteinase 3 (determined by enzyme immunoassay) as a fifth criterion. We excluded patients with active systemic infections, neutropenia ($<$4,000 white blood cells/mm^3), thrombocytopenia ($<$120,000/mm^3), acute or chronic liver dysfunction, malignancy, excessive alcohol use, pregnancy (or breastfeeding), or a history of medical noncompliance.

Trial design. In addition to standard medical therapy for WG, patients were treated with 25 mg etanercept, administered subcutaneously twice a week for 6 months. Etanercept was provided by Immunex Corporation. Conventional immunosuppressive therapies used by patients in this trial included glucocorticoids (GC), CYC, MTX, azathioprine (AZA), and cyclosporine. These therapies were prescribed according to each patient's degree of disease severity at the time of enrollment, and were adjusted as medically indicated based on the patient's clinical status during the trial. Patients were evaluated monthly during the trial, or more often as indicated for clinical care.

Concomitant medications. All patients in the trial received prophylaxis against *Pneumocystis carinii* pneumonia with double-strength trimethoprim-sulfamethoxazole (1 tablet 3 times a week).

Clinical measurements. At each scheduled trial visit and at interval clinical encounters, we collected data on injection site reactions (ISRs), infections, hospitalizations, hemocytopenias, abnormalities evident on liver function tests, and other adverse events. ISRs were graded on a scale of 1–4, with "1" indicating erythema that persisted for at least 4 hours after injection, "2" indicating erythema plus pain, swelling, induration, pruritus, or phlebitis, "3" indicating ulceration, and "4" indicating the need for plastic surgery. Complete blood cell counts as well as serum electrolytes, serum creatinine, albumin, and aspartate and alanine aminotransferase levels were measured at each scheduled visit. Patients receiving CYC had complete blood cell counts checked at least every 2 weeks. Other data collected at each trial visit included the BVAS/WG (see below), a physician's global assessment of disease activity scored on a 100-mm visual analog scale, and the erythrocyte sedimentation rate (ESR).

The BVAS/WG (13), a modification of the original BVAS (15), is an activity index specific for WG. The BVAS/WG consists of evaluations by the clinician of 8 groups of organ system–based items, an additional "general" category that includes arthritis/arthralgias and fever, and space for inclusion of "other" manifestations of active WG. A detailed description of the BVAS/WG, including the evaluation form and a glossary, are accessible on the Internet at http://vasculitis.med.jhu.edu. Assays for ANCA were performed at the Johns Hopkins Immunologic Disorders Laboratory on sera frozen at the entry and 6-month visits. Other clinical outcomes of interest included the achievement of disease remissions (BVAS/WG of 0) and the occurrence of disease flares (increases in the BVAS/WG of at least 1 point) between serial visits during the 6-month period of evaluation.

Statistical analysis. For all 20 patients enrolled, we used paired *t*-tests to compare the mean BVAS/WG scores, physician's global assessments, and prednisone doses at trial entry and 6 months. We also analyzed certain patient subsets separately, for example, the subset of 14 patients for whom etanercept was the only new treatment variable.

RESULTS

Patient characteristics at entry. The patients' clinical characteristics at entry are displayed in Table 1. All of the patients were Caucasian. The mean age was 47 years (range 25–73 years), and there were 9 men and 11 women. Every patient was experiencing either a recent disease flare or had persistently active WG at the time of

Table 1. Patient characteristics at entry*

No. of patients enrolled	20
Male:female ratio	9:11
Mean age, years (range)	46.7 (25–73)
New diagnosis of WG, no. (%)	0 (0)
Time since original WG diagnosis, months (range)	63.6 (14–189)
Previous achievement of remission, no. (%)	6 (30)
Mean BVAS/WG (range)	3.6 (1–8)
Mean PGA of disease activity, mm (scale)	33.7 (0–100)
Features of disease, no. (%)	
Upper respiratory involvement	16 (80)
Arthritis	9 (45)
Conductive hearing loss	4 (20)
Glomerulonephritis	4 (20)
Lung involvement	
Pulmonary nodules	2 (10)
Alveolar hemorrhage	1 (5)
Endobronchial disease	1 (5)
Eye involvement	
Retro-bulbar mass	2 (10)
Conjunctivitis	1 (5)
Mesenteric vasculitis	2 (10)
Meningeal involvement	2 (10)
Cutaneous vasculitis	2 (10)
Fever	1 (5)
Mean ESR, mm/hour (range)	32 (1–90)
Other immunosuppression, no. (%) ever/ no. (%) at entry	
Prednisone	20 (100)/18 (90)
Methotrexate	16 (80)/9 (45)
Cyclophosphamide	12 (60)/6 (30)
Azathioprine	8 (40)/4 (20)
Cyclosporine†	1 (5)/1 (5)

* WG = Wegener's granulomatosis; BVAS/WG = Birmingham Vasculitis Activity Score for WG (13); PGA = physician's global assessment; ESR = erythrocyte sedimentation rate.
† Patient was receiving cyclosporine for a living-related renal allograft.

entry (no patients had newly diagnosed WG). The mean time since the original diagnosis of WG was 64 months (range 14–189 months). Prior to trial entry, 14 of the patients (70%) had never achieved disease remissions that permitted the successful discontinuation of GC. At entry, 4 patients (20%) had severe WG, defined as disease that constituted an immediate threat to either vital organ function or the patient's life (all 4 had glomerulonephritis). Two of the patients with severe disease (10%) also had mesenteric vasculitis, and 1 (5%) had pulmonary hemorrhage. The highest serum creatinine level at the time of enrollment was 2.6 mg/dl (mean 1.1 mg/dl).

The patients' concomitant immunosuppressive medications are displayed in Table 1. Etanercept was added as the only new therapeutic variable in 14 patients (70%); i.e., there were no increases in the doses of GC or other immunosuppressive agents for these patients at the time etanercept was begun. Eighteen of the 20 patients (90%) were receiving GC at the start of the trial. Nine patients (45%) were receiving MTX, 6 (30%) were receiving CYC, 4 (20%) were receiving AZA, and 1 (5%) was receiving cyclosporine (for immunosuppression following renal transplantation) upon entry into the trial.

The mean BVAS/WG at entry was 3.6 (range 1–8), and the mean physician's global assessment of disease activity was 33.7 mm (range 8–84 mm) on a scale of 0–100 mm. The mean ESR at entry was 32 mm/hour. Fourteen of the patients (70%) were ANCA positive by immunofluorescence at entry (12 with cytoplasmic ANCA, 2 with perinuclear ANCA), of whom 11 patients (55%) were positive by enzyme-linked immunosorbent assay (all anti–proteinase 3 positive).

Side effects, withdrawals, and compliance (Table 2). All patients were followed up for a minimum of 6 months. No patients were lost to followup. At 6 months, 19 (95%) were still taking etanercept (the single exception being a patient who developed progression of orbital [retro-bulbar] disease at 4 months of treatment). ISRs were the most common adverse event; 8 ISRs occurred in 5 patients (25% of patients; <1% of all injections). All of the ISRs were mild, being rated as grade 1 (erythema only) in 7 patients or grade 2 (erythema plus mild induration) in 1 patient. Two patients were hospitalized during the course of this trial, 1 of whom had pneumococcal tracheobronchitis. The other hospitalized patient had a total of 4 admissions related to malignant hypertension, hypertensive seizures, and evaluation of advancing renal disease. None of the hospitalizations were related clearly to adverse effects of etanercept. There were 5 episodes of neutropenia and 1 case of elevated serum liver transaminase levels, all of which resolved following reductions in the doses of either CYC or MTX. There were no episodes of pancytopenia, and no neurologic complications in this trial. One patient reported sleep disturbances after starting etanercept.

The patient with pneumococcal tracheobronchi-

Table 2. Adverse events

Event	No. of events	No. of patients
Injection site reactions	8	5
Infections	2*	1
Hospitalizations	5	2
Elevated liver transaminases	1	1
Cytopenias	5	5
Sleep disturbances	1	1

* Includes pneumococcal tracheobronchitis and a localized *Herpes zoster* infection in the same patient.

Table 3. Treatment effects*

Outcome	All patients (n = 20)			Patients with etanercept as only new treatment variable (n = 14)		
	Value	*P*	95% CI	Value	*P*	95% CI
Change in BVAS/WG, entry to 6 months	−3.0	<0.001	−4.0, −2.1	−3.14	<0.001	−4.5, −1.8
Change in PGA, mm	−25.3	<0.001	−36.7, −13.9	−21.8	0.01	−37.4, −6.2
Change in mean daily prednisone dose, mg	−11.6	0.023	−21.3, −1.8	−6.5	0.19	−16.6, +3.6
Number (%) with BVAS/WG of 0 at 6 months	12 (60)	–	–	9 (64)	–	–

* 95% CI = 95% confidence interval (see Table 1 for other definitions).

tis had severe subglottic stenosis caused by WG and was treated simultaneously with CYC (200 mg/day) and prednisone (12.5 mg/day). She developed tracheobronchitis ~2 weeks after entry, but recovered uneventfully and completed the trial. At month 6, she developed a localized *Herpes zoster* infection that was treated successfully with acyclovir. Neither episode of infection was associated with neutropenia.

Treatment effects (Table 3). Nineteen of the 20 patients (95%) improved at least temporarily during this trial, and 16 (80%) achieved BVAS/WG scores of 0 at some point during the period of observation. At 6 months, the mean BVAS/WG score declined 3.0 points, to 0.6 ($P < 0.001$, 95% confidence interval [95% CI] −4.0 to −2.1). Among the 14 patients for whom etanercept was the only new treatment variable, the mean BVAS/WG score declined 3.14 points, to 0.4 ($P < 0.001$, 95% CI −4.5 to −1.8). Five of these 14 patients (36%) achieved and maintained disease remissions (BVAS/WG of 0) throughout the 6-month treatment period. Two of the 14 patients (14%) were able to taper off prednisone entirely. The mean physician's global assessment of disease activity for these 14 patients declined from 29.8 mm to 8.0 mm from trial entry to 6 months, a change of −21.8 mm ($P < 0.01$, 95% CI −37.4 to −6.2). The mean ESR, 32 mm/hour at entry, was unchanged at followup (31 mm/hour). ANCA titers bore no consistent relationship to treatment responses in this study.

Intermittent disease activity was common in this trial. Fifteen patients (75%) had some increase in BVAS/WG scores over consecutive trial visits. In 10 of these patients, the worsening of disease manifestations was minor, with increases in the BVAS/WG of 1.0 compared with that in the previous visit. Five patients had increases in the BVAS/WG of at least 2.0 points over their lowest BVAS/WG score achieved. Three flares were characterized as severe (i.e., potentially threatening to a patient's critical organs or life). One of these flares involved the development of glomerulonephritis and mesenteric vasculitis, and 2 flares involved recurrent orbital disease.

The patient with the highest serum creatinine level at trial entry progressed to end-stage renal disease during this trial and began hemodialysis. The results of a kidney biopsy during the course of her decline in renal function implicated a combination of factors in her renal failure, principally the effects of severe hypertension superimposed on damage from previously active WG. Although no glomerular inflammation was evident in the kidney biopsy specimen, we could not exclude some contribution of active WG to the mild-to-moderate tubulointerstitial inflammation present on the biopsy specimen.

The mean daily prednisone dose for all patients in the trial decreased from 19 mg at entry to 7.4 mg at 6 months, a mean change of −11.6 mg ($P = 0.023$, 95% CI −21.3 to −1.8). Among the 14 patients in whom etanercept was the only new treatment variable, the mean daily prednisone dose at 6 months was 6.4 mg compared with 12.9 mg at entry, a change of −6.5 mg. This comparison did not achieve statistical significance ($P = 0.19$, 95% CI −16.6 to +3.6). No clear patterns in either the reduction or increase in other immunosuppressive medications were observed in this 6-month study.

DISCUSSION

We conducted this open-label trial of etanercept combined with standard therapies for WG to evaluate the safety of these combinations in this disease before conducting a larger trial of treatment efficacy. Despite the immunosuppressive nature of the treatments used in conjunction with etanercept in this trial, we observed few serious adverse events. Etanercept was implicated directly only in the occurrence of ISRs. The frequency of ISRs in this trial (occurring in 25% of the patients enrolled) was comparable with the frequency reported in rheumatoid arthritis trials (5,6). None of the ISRs in this trial were severe.

We anticipated occasional episodes of neutropenia (n = 5) and serum transaminase elevation (n = 1) in this trial because of the frequency with which CYC, MTX, and AZA were used. Although the frequency of adverse events in this study was not directly comparable with that in other longitudinal studies of WG treatment (because of the absence of a standard protocol for the use of conventional agents in this study), the frequencies of neutropenic events and serum transaminase elevations in this study were similar to those in previous studies of CYC (1) and MTX (2) in the treatment of WG. In all cases in this study, neutropenia and serum transaminase elevations resolved upon dose reductions of these conventional agents. In this limited experience, therefore, etanercept did not appear to increase or exacerbate the occurrence of neutropenia. Similarly, the number of hospitalizations (n = 5) was not surprising for a group of patients with WG. No hospitalizations were directly attributable to etanercept side effects.

Opportunistic infections are a common problem in the treatment of WG in treatment regimens using either CYC or MTX (1,2,16). In a study comparing oral and intravenous CYC administration, 54% of all patients enrolled developed opportunistic infections (16). The small number of infectious complications observed in this short trial was reassuring. Although etanercept has been used safely with MTX in patients with rheumatoid arthritis (5), there have been no previous reports of the combined use of CYC and etanercept. In this study, the 6 patients who received CYC and etanercept simultaneously tolerated the combination well from the standpoint of infections. Clearly, however, more experience with the use of these agents together is required before conclusions can be drawn about safety and toxicity.

Definitive statements regarding the efficacy of etanercept in WG are not possible from this trial. Because our aim was to gain experience with the use and safety of etanercept plus conventional treatments in WG, we enrolled patients receiving a broad range of immunosuppressive treatments. Ninety percent received GC concomitantly with etanercept, and 90% also received CYC, MTX, or AZA. Because all patients in the trial received other immunosuppressive therapies, and because there was no comparison group (i.e., a group receiving placebo in addition to conventional therapies for WG), evaluating the impact of etanercept alone on disease activity is difficult. An accurate assessment of the therapeutic potential of etanercept in WG will require a randomized, double-masked, placebo-controlled trial.

The design of this trial probably led to an overestimation of the potential steroid-sparing effect of etanercept. Six patients had been given substantial increases in their prednisone doses at the time etanercept was initiated, and thus they entered the trial on doses of prednisone that would have been intolerable over the long term. The mean decrease in prednisone doses over the 6-month observation period therefore reflects (in part, at least) the phenomenon of regression to the mean. Among the 14 patients in whom etanercept was the only change in treatment at trial entry, the difference in mean daily prednisone at 6 months was not significant.

An often striking effect of etanercept in inflammatory arthritis is a dramatic improvement in the patients' sense of well-being. We observed this phenomenon in a number of patients in this trial. However, objective evaluation of this observation is difficult because of the simultaneous use of other medications and the possible contribution of a placebo effect. One patient felt substantial improvement in her sense of well-being, and yet was 1 of 3 patients in the trial to experience a severe flare (glomerulonephritis) while receiving etanercept.

In conclusion, etanercept combined with standard treatments for WG was well-tolerated. The results of this open-label trial support the performance of a multicenter, randomized, double-masked, placebo-controlled trial of etanercept plus standard therapy in WG. Enrollment for such a trial recently began at 8 centers in the United States.

REFERENCES

1. Hoffman G, Kerr G, Leavitt R, Hallahan C, Lebovics R, Travis W, et al. Wegener's granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116:488–98.
2. Sneller MC, Hoffman GS, Talar-Williams C, Kerr GS, Hallahan CW, Fauci AS. An analysis of forty-two Wegener's granulomatosis patients treated with methotrexate and prednisone. Arthritis Rheum 1995;38:608–13.
3. Stone J, Tun W, Hellmann D. Treatment of non-life threatening Wegener's granulomatosis with methotrexate and daily prednisone as the initial therapy of choice. J Rheumatol 1999;26:1134–9.
4. Mohler K, Torrance D, Smith C, Goodwin R, Stremler K, Fung V, et al. Soluble tumor necrosis factor receptors are effective therapeutic agents in lethal endotoxemia and function simultaneously as both TNF carriers and TNF antagonists. J Immunol 1993;151: 1548–61.
5. Weinblatt M, Kremer J, Bankhurst A, Bulpitt K, Fleischmann R, Fox R, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340:253–9.
6. Moreland L, Schiff M, Baumgartner S, Tindall E, Fleischmann R, Bulpitt K, et al. Etanercept therapy in rheumatoid arthritis: a randomized, controlled trial. Ann Intern Med 1999;130:478–86.

7. Kindler V, Sappino A, Grau G, Piguet P, Vassalli P. The inducing role of tumor necrosis factor in the development of bactericidal granulomas during BCG infection. Cell 1989;56:731–40.
8. Deguchi Y, Shibata N, Kishimoto S. Enhanced expression of the tumour necrosis factor/cachectin gene in peripheral blood mononuclear cells from patients with systemic vasculitis. Clin Exp Immunol 1990;81:311–4.
9. Ludviksson B, Sneller M, Chua K, Talar-Williams C, Langford C, Ehrhardt R, 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.
10. Nassonov E, Samsonov M, Tilz G, Beketova T, Semenkova E, Baranov A, 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.
11. Noronha I, 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.
12. Falk R, Hogan S, Carey T, Jennette J, for the Glomerular Diseases Network. Clinical course of anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and systemic vasculitis. Ann Intern Med 1990;11:656–63.
13. Stone JH, Hoffman GS, Merkel PA, Min Y-I, Uhlfelder ML, Hellmann DB, et al. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. Arthritis Rheum 2001;44:912–20.
14. Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101–7.
15. Luqmani R, Bacon P, Moots R, Janssen B, Pall A, Emery P, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. QJM 1994;87:671–8.
16. Guillevin L, Cordier J-F, Lhote F, Cohen P, Jarrousse B, Royer I, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. Arthritis Rheum 1997;40:2187–98.