Longterm Safety and Efficacy of Etanercept in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Patients with rheumatoid arthritis (RA) treated with etanercept (Enbrel®) in controlled studies of 3 to 6 months' duration had rapid and sustained improvement of their disease, with minimal safety issues. In this study, we examine safety and clinical benefit after longer term treatment with etanercept.

Methods. All adult patients with RA with a previously inadequate response to one or more disease modifying antirheumatic drugs, and who received at least one dose of etanercept as monotherapy in controlled or open label clinical trials were evaluated for safety and clinical benefit. Adverse event rates were compared as was evidence of continued benefit over time.

Results. Etanercept continued to be safe and well tolerated in 628 adult patients treated for a median of 25 mo (maximum 43 mo; 1109 patient-years). Nine percent of patients withdrew due to lack of efficacy and 7% due to adverse events. Most adverse events were mild, and no statistically significant increases in frequency of events were seen when patients received etanercept over longer periods of time. Clinical benefit was maintained with longterm therapy. A 100% improvement in individual disease activity measures was achieved by 17% to 28% of the patients. Fifty-five percent of patients who were taking corticosteroids (mean dose at baseline 6.6 mg/day) decreased or discontinued corticosteroid therapy while maintaining control of their arthritis symptoms.

Conclusion. Etanercept continued to be safe and well tolerated, and its clinical benefit was sustained for a median of 25 mo and for as long as 43 mo in patients with RA. (J Rheumatol 2001;28:1238–44)

Key Indexing Terms:
RHEUMATOID ARTHRITIS TUMOR NECROSIS FACTOR RECEPTOR ETANERCEPT

Etanercept (Enbrel®) is a competitive inhibitor of tumor necrosis factor (TNF) and contains fully human TNF receptors. These soluble TNF receptors bind and neutralize the biologic activity of TNF, a proinflammatory cytokine that has a complex role in the pathogenesis of rheumatoid arthritis (RA). Initial studies of etanercept in patients with RA concentrated on the safety and activity of etanercept in patients with active RA who had an inadequate response to one or more available disease modifying antirheumatic drugs (DMARD). Controlled studies were conducted with etanercept alone or in combination with methotrexate. These trials found etanercept to be safe and effective over treatment periods of 3 to 6 months[1-3].

Despite an excellent safety profile, concern exists that there may be an increased incidence of certain adverse events, particularly serious infection[4-6] or malignancies[7-10], with more prolonged inhibition of TNF activity. To assess continued safety and efficacy with chronic etanercept treatment, patients were additionally evaluated in an open label longterm study.

MATERIALS AND METHODS

Patients. All adult RA patients with a previously inadequate response to one or more DMARD and who received at least one dose of etanercept as monotherapy in any of 3 double blinded placebo controlled studies[1-3], one open label pharmacokinetic study, and 2 open label safety studies were eligible to enroll in the longterm open label study. Figure 1 depicts the movement of patients through multiple studies. Inclusion criteria in the controlled studies have been described and were similar in the other trials.

Methods. Included in this analysis were all available data from all patients who received etanercept as monotherapy in any of the above clinical trials. Patients who participated in multiple studies were only counted once. In placebo controlled and other early studies of etanercept, patients were assessed at least once monthly. In the longterm, open label study, patients

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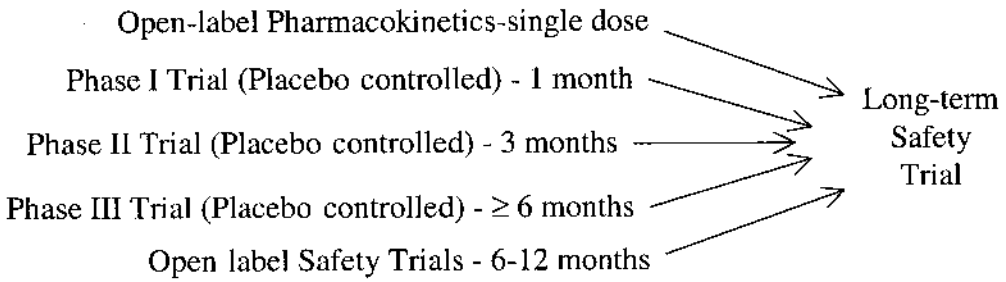

Figure 1. The movement of patients with RA through multiple studies.

were assessed every 3 to 4 mo. Evaluations included vital signs and physical examinations, hematology and chemistry profiles, urinalysis, and assessment of adverse events. Data on non-serious adverse events were collected during all exposure in 6 of the studies and during the first 12 months of therapy in the longterm study. After 12 mo, non-serious adverse events were not recorded since interim experience showed that rates of these events in the longterm study were less, in most cases, than in the controlled studies. Serious or potentially serious adverse events, defined as life threatening or requiring hospitalization, medical or surgical intervention, or intravenous (IV) antibiotics, were recorded over the total exposure to etanercept.

Adverse events and serious adverse events per patient-year were calculated as total numbers in each event category reported on or after the first dose date divided by total time taking drug (summed over patients). Total time taking drug was computed in days and then divided by 365 to obtain patient-years, from the first dose in the initial study to the last dose in the longterm study, excluding gaps between studies. Events per patient-year in specified time intervals were calculated as total number of events beginning during a particular time interval divided by total time taking drug (summed over patients) within that time interval. In the comparison of rates in controlled studies with rates in the longterm study, p values < 0.10 were considered statistically significant. All available safety data were used, up to 43 mo of etanercept therapy.

Efficacy data are presented for all patients who received etanercept therapy, excluding experience from the earliest controlled and pharmacokinetics trials where patients could not immediately enroll in the longterm study. Disease activity measures, including tender and swollen joint counts, C-reactive protein (CRP), and disability as measured by responses on the Health Assessment Questionnaire (HAQ), were recorded at each visit. Clinical benefit data were pooled over all doses and over both controlled and open label trials and were displayed over time, using data from the longterm study and from those studies that allowed direct enrollment into the longterm study.

RESULTS

Exposure. Six hundred twenty-eight adults with RA received etanercept as monotherapy in 7 clinical studies. Of the 628 patients, 479 have received etanercept for at least 12 mo, 444 for at least 18 mo, 334 for at least 24 mo, 139 for at least 30 mo, and 53 for 36 to 43 mo. Four hundred eighteen patients (67%) continue to receive etanercept in this ongoing clinical trial. The reasons for discontinuation from etanercept therapy were as follows: 9% of patients withdrew due to lack of efficacy; 8% were lost to followup (e.g., during extended time periods between the earliest trials and later open label trials); 7% withdrew due to adverse events; 6% requested to discontinue; and the remainder (3%) withdrew due to physician decision or protocol requirements or violations.

The dose of etanercept ranged from 0.25 mg/m^2 (in early trials) to the recommended dose, 25 mg administered subcutaneously (SC) twice weekly. Five hundred thirty-six patients (85%) received 25 mg etanercept administered SC twice weekly for most of their time on therapy.

For non-serious adverse events, the mean (median) total exposure to etanercept was 15 (17) mo, representing 796 patient-years. For serious or potentially serious adverse events, the mean (median) total exposure to etanercept was 21 (25) mo, representing 1109 patient-years.

Patient population. Demographic and clinical characteristics of these patients at the time of their first dose of etanercept are summarized in Table 1; 78% of patients were female; the mean age was 53 years. Most patients had longstanding active RA, with a mean disease duration of 12 years, a mean tender joint count of 32, and mean swollen joint count of 26.

Safety. Etanercept was well tolerated during extended therapy and adverse events were similar to data from controlled trials (Table 2). Injection site reactions were the only events that

Table 1. Demographic and disease history at baseline of earliest study.

Characteristic	Adults, N = 628
Sex, n (%)	
Female	489 (78)
Male	139 (22)
Race, n (%)	
Caucasian	576 (92)
African American	18 (3)
Hispanic	15 (2)
Asian	12 (2)
Other	7 (1)
Age, yrs	
Mean	53
Range	18–86
Mean duration of RA, yrs	12
Range	0–58
Mean number of prior DMARD	3.3
Range	1–8
Concomitant therapy, %	
Corticosteroids	58
Nonsteroidal antiinflammatory drugs	61

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Table 2. Rates of adverse events* in controlled trials compared to rates with longterm etanercept therapy†.

Event	Controlled Trials: Placebo (n = 152), Event/Patient yr	Controlled Trials: Etanercept (n = 349), Event/Patient yr	Longterm Therapy (n = 628), Event, yr
Injection site reaction	0.62	7.73¶	N/A**
Upper respiratory infection ("colds")††	0.68	0.82	0.46
Headache	0.62	0.68	0.27
Sinusitis††	0.42	0.31	0.19
Rash	0.12	0.21	0.18
Nausea	0.47	0.30	0.14
Cystitis††	0.06	0.17	0.12
Rhinitis (noninfectious)	0.35	0.45	0.13
Skin infection ††	0.30	0.16	0.14
Diarrhea	0.35	0.27	0.13
Bronchitis††	0.12	0.10	0.11
Flu syndrome††	0.18	0.16	0.11
Pain	0.22	0.18	0.11
Abdominal pain	0.12	0.17	0.09

*Adverse events of > 10% of any group displayed on the table.
†Median time for followup of non-serious adverse events was 17 mo (maximum 32 mo).
¶p value relative to placebo < 0.001.
**Injection site reactions were not required to be reported after 3 mo in the longterm study.
††Infection data from patients in early studies are not included due to different data collection methods. For infections, data were collected on the following numbers of patients: in controlled trials, placebo = 110 and etanercept = 213; in longterm therapy, n = 577.

occurred significantly more frequently in etanercept patients than in placebo patients in controlled trials ($p < 0.001$). The rates of non-serious adverse events were no greater in any category in the longterm analysis compared to those reported in either the placebo or etanercept groups in the controlled studies.

No increase was observed in the rate of more serious events in the longterm analysis compared to those reported in controlled studies (Table 3). Deaths occurred at a rate of 0.9 per 100 patient-years. Of eleven deaths in the 628 patients, 5 patients died of cardiac disease (myocardial infarction or sudden death). Two patients died of cancer (lung and ovarian). One patient died of sepsis after staphylococcal septic arthritis. One patient died of a retroperitoneal bleed 11 days after surgery. One patient died of a presumed infection, but no cultures were ever positive. Another patient died of injuries sustained in an accident.

No increase was observed in the rate of non-serious or serious infections with extended exposure to etanercept. Most infections were typical bacterial infections (staphylococcal or streptococcal) or were self-reported with no cultures obtained. Fifty-three potentially serious infections, those requiring hospitalization or IV antibiotics, occurred in 43 patients, at a rate of 0.048 infections per patient-year. After successful resolution of their infections, 79% (34/43) of these patients have continued to receive etanercept. No patient developed an opportunistic infection. No patient developed systemic lupus erythematosus or any other new autoimmune rheumatic disease.

Malignancy was reported in 8 patients treated with etanercept. No predominant cancer type was observed: ovarian cancer (n = 2); lung cancer (n = 2); and one occurrence each of breast, prostate, bile duct cancer, and Hodgkin's disease. No increase was seen in the rate of malignancies with etaner-

Table 3. Serious adverse events in controlled trials compared to longterm etanercept therapy.

Event	Controlled Trials: Placebo (n = 152) Event/Patient-yr	Controlled Trials: Etanercept (n = 349) Event/Patient-yr	Longterm Therapy: Etanercept (n = 628) Event/Patient-yr
Death	0.025	0	0.01
Noninfectious adverse event	0.20	0.13	0.15
Infection	0.050	0.043	0.048

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cept therapy compared to that expected in the general population (10.7 cases expected), when calculated using age and sex matched rates from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database[11].

Clinical benefit. In reports of etanercept therapy in patients with RA, tender and swollen joint counts have been shown to improve rapidly[1-3]. This improvement was sustained during longterm therapy, with median counts of 4 tender joints and 5 swollen joints at 30 mo (Figure 2). Similarly, CRP levels normalized rapidly and remained in the normal range (median 0.7 mg/dl, Figure 3).

The American College of Rheumatology preliminary criteria for improvement in RA (ACR20) was achieved by 60% of patients at 3 mo and by 73% of patients at 30 mo. Similarly, 50% of patients achieved the ACR50 and 26% achieved the ACR70 at 30 mo.

In an intent-to-treat analysis, 64% of patients receiving 25 mg etanercept achieved the ACR20 at their most recent visit.

Substantial numbers of patients achieved 100% improvement in individual disease activity measures during extended etanercept therapy (Figure 4). At 30 mo, 28% of patients had no tender joints, 27% had no swollen joints, and 17% had no tender or swollen joints. Also at 30 mo, 18% had disability scores of zero, as determined by their responses to the HAQ.

About half the patients (54%) were receiving corticosteroids (≤ 10 mg/day prednisone or equivalent, mean dose 6.6 mg) upon initiation of etanercept therapy; during initial trials, no change in corticosteroid dose was allowed. At the beginning of the longterm trial, 338 patients were receiving corticosteroids and were permitted to taper their corticosteroid doses at the discretion of their physician. Fifty-five percent of these patients decreased their corticosteroid dose by a mean of 70% (4.4 mg), and 25% discontinued corticosteroids completely. Six percent of patients in this study had an increase in their corticosteroid dose. Clinical response to etanercept was maintained despite the decrease or discontinuation in corticosteroids.

DISCUSSION

Controlled studies have shown that etanercept is an effective therapy for RA and has an excellent safety profile. This report presents cumulative data on the effects of etanercept in RA and demonstrates the continuing safety of etanercept with longer exposure. Adverse effects observed with prolonged etanercept exposure in 628 adult patients (up to 43 months; 1109 patient-years) are no more frequent, severe, or different than those observed in the controlled studies.

TNF is a proinflammatory cytokine that has been shown to play a key role in the pathogenesis of RA[12]. It also has a multitude of biological effects that include participation in the immunologic defense against infection. Although the role of TNF in host defense against infection is complex, it appears that the presence of this cytokine is important to the outcome of infections[4-6,13], and the complete absence of TNF is associated with poorer outcome. However, these preclinical

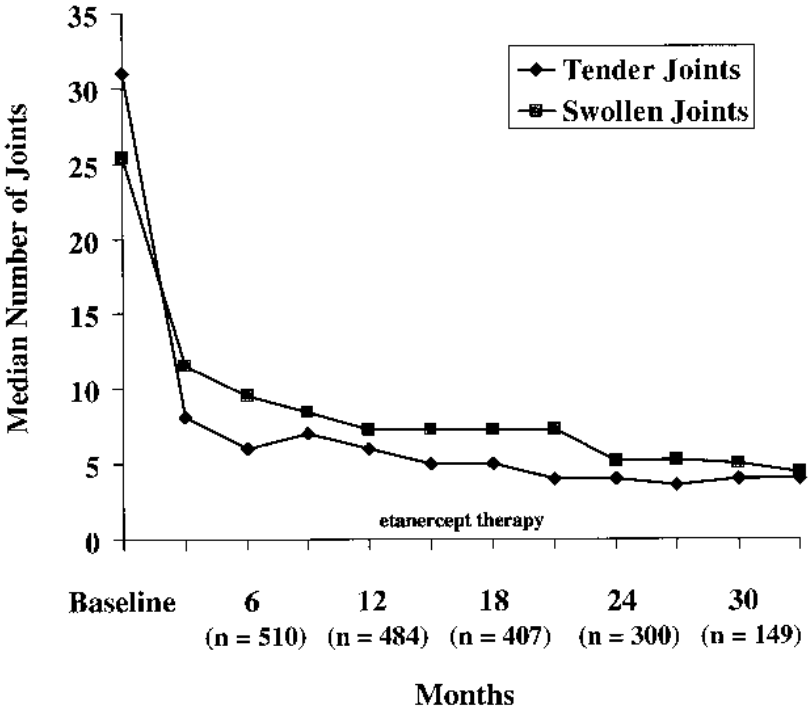

Figure 2. Tender and swollen joint counts decreased rapidly and remained stable over time.

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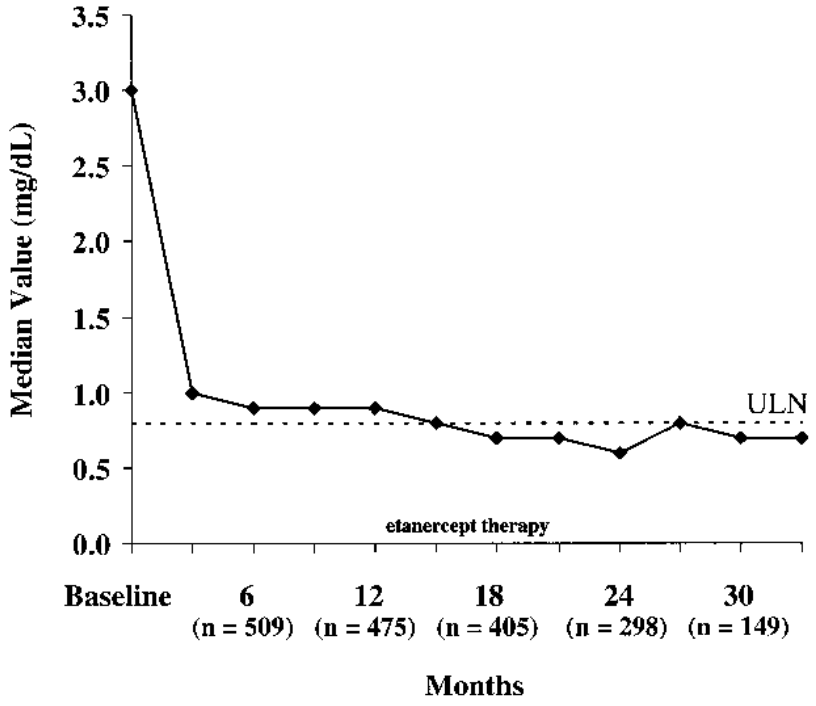

Figure 3. CRP levels rapidly returned to normal range and remained stable over time. ULN: upper limit of normal (0.8 mg/dl).

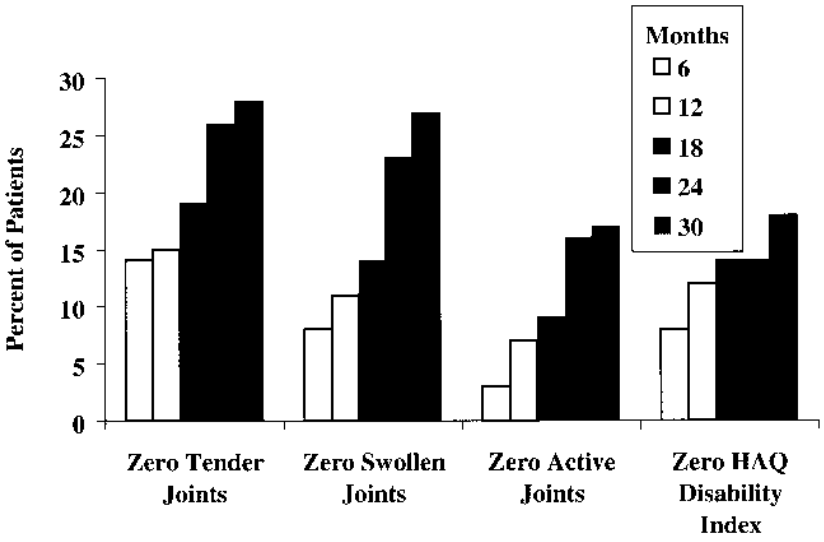

Figure 4. Many patients achieved 100% improvement of disease variables during the study.

concerns have not been corroborated in clinical experience with etanercept. One possible explanation of this observation is that patients with RA have increased levels of TNF, and therapy with etanercept, a competitive inhibitor, may be establishing more normal TNF levels rather than ablating its function altogether.

Controlled trials have shown that the rates of infection and serious infection are similar in placebo treated and etanercept treated patients. Further, the observations in the longterm study show that, with longer etanercept treatment, the rate and severity of infection is no greater than observed in the placebo group in the controlled trials. Of the patients who developed a potentially serious infection, the majority (79%, 34/43) continue taking etanercept therapy. No patient developed an opportunistic infection. The rate of infection associated mortality (2 patients, one with a documented infection and the second presumed; 0.18 patients per 100 patient-years) is low and compares favorably to rates in the literature (Table 4).

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Table 4. Comparative rates of infection associated mortality in patients with RA.

Database	Total Patient-yrs	No. Deaths due to Infection	Percentage of Patients	Event Rate per 100 Patient-yrs
Etanercept				
All DMARD refractory RA patients	1109	2	0.3	0.18
Literature				
van den Borne[21]	2280	9	2.2	0.39
Prior[22]	5012	32	7.1	0.64
Duthie[23]	2240	11	3.6	0.49

Additionally, patients receiving commercial etanercept have spontaneously reported infections at rates similar to those observed in the clinical trials[14].

Another biological effect of interest with TNF is its potential effect on tumor development. Early studies indicated that TNF was cytotoxic for certain tumor lines[15] and caused necrosis of experimental tumors[16,17]. However, there is increasing evidence that TNF is a growth factor for certain malignancies, including multiple myeloma[18], leukemias[19,20], lymphomas[8], skin cancer[10], and ovarian cancer[9]. Additionally, TNF may enhance the metastatic potential of tumors[7]. Analysis of genotypes in patients with lymphoma revealed that those with polymorphisms associated with greater production of TNF had greater first-line treatment failure, shorter progression-free survival, and poorer overall survival rates[8]. To determine the effect of TNF inhibitors on the risk of malignancy over time, longterm followup studies are needed.

No increase in the incidence of malignancies has been observed with up to 43 months of etanercept exposure. Eight malignancies were reported in adults treated with etanercept, consistent with the 10.7 expected in the age and sex matched general population using projections from the NCI SEER database. As it may take 5 to 10 years to note an effect on malignancy rates, observation of these patients continues.

Corticosteroid usage is associated with osteoporosis and with events such as hip fracture in a dose related manner. Patients with RA reduce their risk of hip fracture by 2.5% for every 1 mg/day reduction of prednisone[24]. Other steroid induced toxicities may behave similarly. Most patients who were taking concomitant corticosteroids in this study achieved significant clinical benefit from etanercept and additionally decreased their corticosteroid usage, an extra safety benefit for these patients. Etanercept continues to be safe and well tolerated and provides clinical benefit over extended treatment periods for patients with RA.

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