Etanercept Treatment in Adults with Established Rheumatoid Arthritis: 7 Years of Clinical Experience

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ABSTRACT. ***Objective***. To evaluate safety and efficacy of longterm etanercept treatment in patients with disease modifying antirheumatic drug (DMARD) refractory rheumatoid arthritis (RA).

Methods. Safety results are reported for 714 patients who received etanercept in one of 7 initial trials or a longterm extension. Efficacy results are reported for 581 patients who enrolled in the extension.

Results. Of the 714 patients enrolled in the initial trials, 581 (81%) enrolled in the extension, and 388 (54%) patients are continuing to receive etanercept therapy. The longest individual treatment was 8.2 years, with 3139 total patient-years of etanercept exposure. Rates of serious adverse events (overall rate = 14.8 events/100 patient-yrs), serious infections (overall rate = 4.2 events/100 patient-yrs), cancer (overall rate = 1.0 events/100 patient-yrs), and deaths (overall rate = 0.7 events/100 patient-yrs) were stable each year, through 8 years of etanercept exposure. For 356 patients who completed 6 years of etanercept treatment, response rates were ACR20 = 73%, ACR50 = 52%, ACR70 = 27%, DAS28 CRP good response = 52%, and DAS28 CRP remission = 37% of patients. Similar responses occurred in 167 patients who completed Year 7. Doses of concomitant methotrexate or corticosteroids were reduced in many patients who maintained clinical responses.

Conclusion. The safety profile of etanercept was consistent over time, with rates of adverse events similar to those reported for patients with RA in general. Durable clinical responses were observed in some patients for 7 years or more. The benefit-to-risk ratio for longterm etanercept treatment remains highly favorable. (First Release Mar 15 2006; J Rheumatol 2006;33:854–61)

Key Indexing Terms:
ETANERCEPT RHEUMATOID ARTHRITIS LONGTERM TREATMENT

Rheumatoid arthritis (RA) is a chronic illness characterized by joint inflammation that leads to joint destruction, functional impairment, and reduced quality of life for patients with moderate to severe disease[1-3]. Treatment goals are longterm substantial relief of signs and symptoms of joint inflammation including pain, arrested joint damage, and improved function[4]. Ideally, treatment will induce disease remission and restore normal functionality.

Currently accepted treatment options for RA include nonbiologic disease modifying antirheumatic drugs (DMARD) and biologic therapies, the latter often combined with methotrexate (MTX) therapy[5]. Tumor necrosis factor (TNF) inhibitors have been shown to significantly reduce the progression of joint damage[6-9] and ensure longterm symptomatic relief of RA, as measured by the American College of Rheumatology (ACR) responses, disease activity scores (DAS), and Health Assessment Questionnaires (HAQ)[7]. Because of the chronic nature of RA, the longterm safety and efficacy profile of TNF inhibitors such as etanercept is of interest to both patients and clinicians.

In controlled trials, etanercept has proved to be safe and efficacious in early RA (disease duration < 3 yrs)[6,10], juvenile rheumatoid arthritis (JRA)[11], and in DMARD-refractory RA[12-14]. At the end of the blinded, controlled phases of clinical trials in adults, etanercept had induced ACR20 responses in 59% to 76% of patients with RA[6,7,12,14,15].

Etanercept has now been used in patients with RA for over 11 years including clinical trials. Patients with DMARD-refractory RA who completed initial etanercept trials were offered the opportunity to continue etanercept treatment in an ongoing open-label extension. Previous examination of these patients after 2 years of etanercept treatment showed that improvements in signs and symptoms seen in the initial double-blind studies were sustained though 2 years of treatment[16,17].

Many of the DMARD-refractory patients with RA who continued in the extension are now in their seventh year of

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etanercept treatment. The objective of this analysis is to evaluate the longterm safety of etanercept and the effects of etanercept on signs and symptoms of joint inflammation, patient function, laboratory measures of systemic inflammation, and concomitant use of MTX and corticosteroids.

MATERIALS AND METHODS

Patients and studies. Seven hundred fourteen adult patients with DMARD-refractory RA were enrolled in one of 7 initial clinical trials, 3 of which were placebo-controlled, randomized, double-blind phase 2 or 3 trials; 2 were phase 1 randomized dose-finding trials, and 2 were open-label. In these initial trials, DMARD-refractory RA was defined as a less than optimal response to at least one DMARD.

The open-label extension was designed to assess extended treatment with etanercept (Enbrel®). Patients who received etanercept or placebo in the initial studies[16] were eligible to receive etanercept in the extension. Followup visits occurred every 3 months during the first year of the extension, then every 4 to 6 months thereafter, with clinical and laboratory data gathered at these times.

Patients continued the etanercept dose that was administered in their original protocol of enrollment, either 10 mg or 25 mg twice a week, for the first year of the extension. Thereafter, patients who received 10 mg twice a week were permitted to receive 25 mg twice a week. All other patients received etanercept 25 mg twice a week throughout the extension.

Patients who were receiving MTX or corticosteroids at a dose of ≤ 10 mg/day of prednisone or its equivalent upon entry to the extension were permitted to continue these medications. After the first year, patients who were not taking DMARD or corticosteroids at the beginning of the extension could add these drugs, at the discretion of the investigator.

The primary objectives of the extension were to evaluate the longterm safety of etanercept, improvement in physical function/disability, and quality of life. Reports of non-serious adverse events were collected during the initial controlled efficacy studies and for the first year of the extension, but not thereafter. Reports of serious adverse events (SAE) were collected during the initial controlled efficacy studies and throughout the extension. SAE were defined as events that were fatal or life-threatening, resulted in permanent or significant disability or incapacity, were a congenital anomaly or birth defect, or required or prolonged inpatient hospitalization. Serious infections were defined as infections requiring hospitalization or intravenous antibiotics. There was no requirement for screening patients for exposure to tuberculosis [purified protein derivative (ppd) testing] before enrollment. SAE were classified using a modified version of the Coding Symbols for a Thesaurus of Adverse Reactions Terms (COSTART) 1990 dictionary[18].

Statistical methods. This analysis included patient visits reported through August 2004. Patients who prematurely discontinued from an initial study or from the extension were not replaced. No imputations or estimation methods were used for missing values during the study.

Baseline demographics and disease history were obtained for each patient at enrollment in the first study in which the patient received etanercept and were summarized descriptively. Changes over time in corticosteroid and nonsteroidal antiinflammatory drug usage were described relative to the baseline dosage at time of first etanercept exposure.

Drug exposure over time from the first dose of etanercept to the most recent drug dose dates available was calculated excluding placebo experience. Time of treatment was assessed in one-year increments. All patients receiving at least one dose of etanercept are included in the Year 1 analysis. Successive years are based on declining numbers of patients, reflecting patient withdrawals from the study or patients who had not achieved the particular timepoint at the time of the data cutoff date for this report.

Safety was assessed for all patients who received at least one dose of etanercept. Safety events with a start date on or after the day each patient received the first dose of etanercept were included. Safety data are summarized by year in which the patient received etanercept, even if the patient did not complete a full year of therapy. For example, a safety event occurring after 1.5 years of therapy was attributed to Year 2. Safety evaluations included exposure to etanercept, occurrence of deaths, malignancies and other SAE, and safety-related discontinuations. Rates of SAE observed in the extension were compared with rates in the original controlled clinical trials and with published rates for healthy or RA patient populations. The total number of patient-years (including gaps between studies) was used to calculate the expectations for rates of deaths.

Efficacy timepoints for patients who received their first dose of etanercept in the initial clinical trials are relative to baseline of the initial trials, except for 8 patients who had an 18-month gap between their initial study and the extension. The timepoints for these 8 patients were determined from the baseline of the extension. The efficacy timepoints for patients who received placebo in their initial clinical trials were related to the baseline of the extension, the study in which they received their first dose of etanercept.

Efficacy was assessed using the ACR response criteria[19] and DAS[20] and are presented as observed cases (i.e., no imputations were done for missing values). DAS28 scores were determined using C-reactive protein (CRP) values[21] instead of erythrocyte sedimentation rates (ESR) because only CRP was measured in all years of the initial clinical trials and the extension. DAS28 CRP good response was defined as improvement from baseline of > 1.2 and achievement of disease activity < 3.2. DAS28 CRP remission was defined as DAS < 2.6, and complete response was defined as zero tender and zero swollen joints. Joint counts were based on assessment of 71 joints for tenderness or pain and 68 joints for swelling. Joints not assessed at baseline were excluded from all future assessments. Additional analyses included the number of swollen and tender joints, ESR, CRP, and HAQ.

RESULTS

Patient enrollment. The schema outlining patient enrollment in the initial clinical trials and the extension is provided in Figure 1. Seven hundred fourteen patients with DMARD-refractory RA received at least one dose of etanercept in the initial clinical trials or the extension (for patients who received placebo in the initial trials). Of these 714 patients, 89 (12%) withdrew from their initial clinical trial and did not enroll in the extension. Another 44 (6%) patients completed their initial clinical trial, but did not enroll in the extension, leaving 581 (81%) patients who enrolled in this study. Of the 581 patients who enrolled in the extension, 237 withdrew, leaving 344 (59%) patients who were continuing to receive etanercept as of the cutoff date for this report. Of a total of 44 sites that enrolled patients in the extension, 3 (7%) ceased participation by August 2004.

Etanercept exposure. All patients received etanercept at 25 mg twice a week in their initial clinical trial or the extension, except for 79 (11%) of the 714 patients who received etanercept at 10 mg twice a week both in their initial clinical trial and for the first year of the extension (after the first year these patients were permitted to switch to 25 mg etanercept). The mean (SD) dose of etanercept in patients in this study was 24.4 (1.9) mg twice a week (range 10 to 25 mg twice a week). The mean duration of etanercept dosing in the 581 patients who enrolled in the extension was 5.1 years (range 28 days to 8.2 yrs). Forty-one percent of patients (241 of 581) completed 6 full years of therapy, and 117 patients (20%) completed 7 full years. There were 603 patient-years of etanercept exposure in the initial studies and 2536 patient-years in the exten-

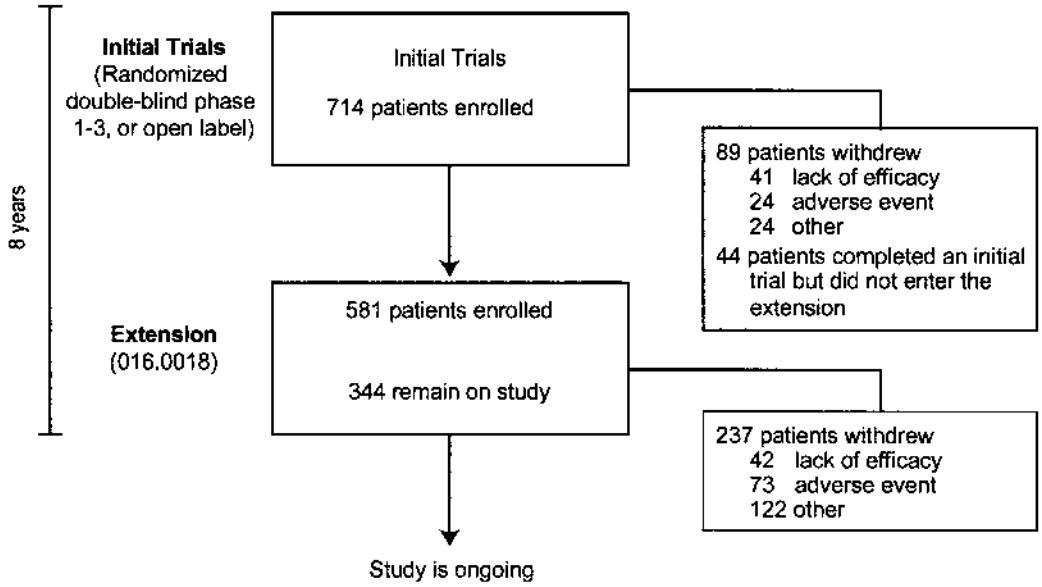

Figure 1. Study sample enrollment and disposition.

sion, for a total of 3139 patient-years of etanercept exposure.

Reasons for patient withdrawal. Withdrawals from the study are displayed in Figure 2, along with the 7 most common reasons for withdrawal. Lack of efficacy was the most frequently cited reason for withdrawal, occurring in 83 (12%) of the 714 patients, with 41 withdrawals over 603 patient-years in the initial clinical trials and 42 withdrawals over 2536 patient-years in the extension. Adverse events and deaths accounted for 97 (14%) withdrawals, with 24 (3%) of these events occurring in the initial clinical trials and 73 (10%) occurring in the extension. Yearly rates of withdrawals for adverse events ranged from 11.2 to 24.5 withdrawals/100 patient-years, into the eighth year of etanercept exposure. Twenty-four patients withdrew from the initial trials and 122 withdrew from the extension for other reasons, including patient refusal [65 (9%)], physician decision [23 (3%)], and protocol issues [14 (2%)]; 12 patients (2%) were lost to followup.

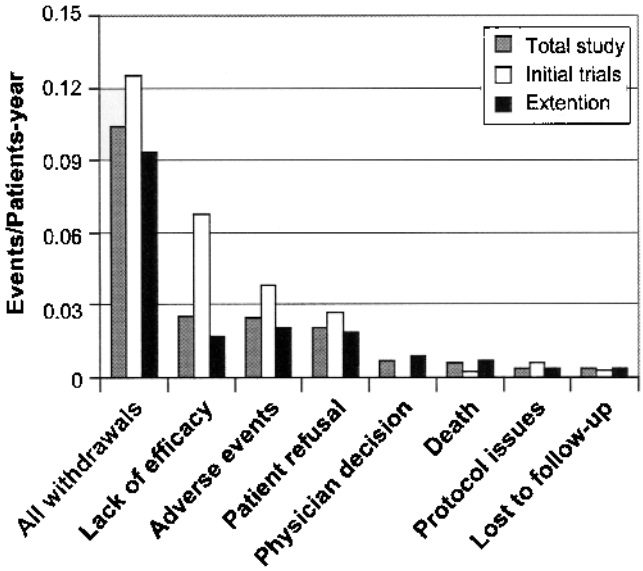

Figure 2. Overall rates of withdrawal from the study and by reason for withdrawal. Rates given for "Total Study" are combined overall rates for the initial trials and the extension.

Patient demographic and disease characteristics. Demographics, disease characteristics, and RA medications were similar between the 714 patients enrolled in the initial clinical trials and the 581 patients who enrolled in the extension (Table 1). Ninety percent of patients were Caucasian, about 80% were women, and the mean age was in the early 50s. Eighty-two percent of patients were seropositive for rheumatoid factor and more than 60% had failed 3 or more DMARD.

Concomitant medications. A total of 208 (36%) patients took

Table 1. Demographic and disease characteristics for all patients enrolled in the initial studies and patients who enrolled in the extension.

	All Patients (n = 714)	Patients Who Entered Extension (n = 581)
Female sex, no. (%)	562 (79)	465 (80)
White, no. (%)	643 (90)	522 (90)
Age, mean (range) yrs	53 (18–86)	52 (18–86)
Duration of RA, mean (range)	12 (0–58)	12 (0–58)
Rheumatoid factor-positive, no. (%)[a]	462/561 (82)	405/491 (82)
Prior DMARD, mean (SD)	3.2 (1.6)	3.3 (1.6)
Methotrexate, no. (%) receiving	85 (12)	79 (14)
Corticosteroids, no. (%) receiving	466 (65)	376 (65)
NSAID, no. (%) receiving	525 (74)	431 (74)

RA: rheumatoid arthritis; DMARD: disease modifying antirheumatic drugs, NSAID: nonsteroidal antiinflammatory drugs. [a] Not all patients were tested for rheumatoid factor at baseline.

at least one dose of MTX at any time from baseline through the seventh year of the extension. Seventy-nine of these patients were receiving MTX at entry into the extension and 129 patients initiated MTX sometime after the end of Year 1 of the extension. All 79 patients who were receiving MTX at entry into the extension came from one of the initial clinical trials that examined etanercept in combination with MTX. At the end of the first year of the extension, 69 of these 79 patients were still in the trial and receiving MTX, 34 had decreased their dose of MTX, and none had increased it. The median dose of MTX decreased from 17.5 mg weekly (range 7.5 to 25 mg weekly) at the beginning of the extension to 15 mg weekly (range 2.5 to 25 mg weekly) at Year 1 of the extension. After Year 1, the proportion of patients taking MTX in any given year was 26% or less, and the median dose remained unchanged.

DMARD including MTX could be added to etanercept after the end of Year 1 of the extension. From the second through seventh year of the extension, a total of 25 (4%) of the 581 patients took at least one dose of leflunomide, 12 (2%) took at least one dose of hydroxychloroquine, and 7 (1%) took at least one dose of sulfasalazine.

Three hundred seventy-six patients (65%) were receiving oral corticosteroids at the start of the extension, with a median dose of 5 mg per day. At the end of the first year of etanercept treatment, 307 of 522 (59%) patients were receiving corticosteroids, with a reduced median dose of 3 mg per day. After the first year, corticosteroids could be added to the therapeutic regimen for patients who were not taking these drugs at the beginning of the extension. From the beginning of year 2 through year 7, an additional 51 patients initiated corticosteroid therapy at any time. However, the overall proportion of patients taking oral corticosteroids decreased steadily from 65% at baseline to 34% at Year 6.

Serious adverse events. SAE were reported by 243 (34%) of the 714 patients, who experienced a total of 466 SAE over the course of the initial clinical trials and the extension. The overall rate of SAE was 14.8/100 patient-years, with a range from 11.2 to 24.5/100 patient-years (Figure 3). The rate of SAE observed in the extension was comparable to the rate observed in the initial controlled efficacy trials, for both the placebo and etanercept groups. In the initial controlled trials, 8 patients out of 152 reported SAE in the placebo group (20.0 events/100 patient-yrs; 40 patient-yrs), and 17 patients out of 349 reported SAE in the etanercept group (15.0 events/100 patient yrs; 117 patient-yrs).

Overall, the most common SAE was bone fracture, which occurred in 23 (3.2%) patients. Seventeen (2.4%) patients had myocardial infarctions. In addition, a variety of cardiovascular events were reported as SAE: 11 patients had congestive heart failure or pulmonary edema, 10 patients each had angina/coronary artery disease or arrhythmia, 5 had cardiac arrest, 3 had syncope, 2 had ruptured aortic aneurysms, and one patient had acute myocarditis. Five patients had cerebrovascular accidents, and 3 of these 5 had 2 events each.

One patient was diagnosed with multiple sclerosis after about 15 months of etanercept exposure. She continued to receive etanercept for about 40 additional months without disease exacerbation, and withdrew from the study to begin treatment with an investigational RA drug.

Serious infections. Ninety-four patients (13%) reported 132 serious infections for a rate of 4.2 events/100 patient-years, with a range from 2.9 to 5.8 serious infections/100 patient-years from Years 1 through 8 (Figure 3). No increase in the rate of serious infections was apparent with increased duration of exposure to etanercept. The most frequent types of infections reported were as follows: pneumonia (21 patients, 22 events, 0.7 events/100 patient-yrs); skin/soft tissue (19 patients, 20 events, 0.6 events/100 patient-yrs); and septic

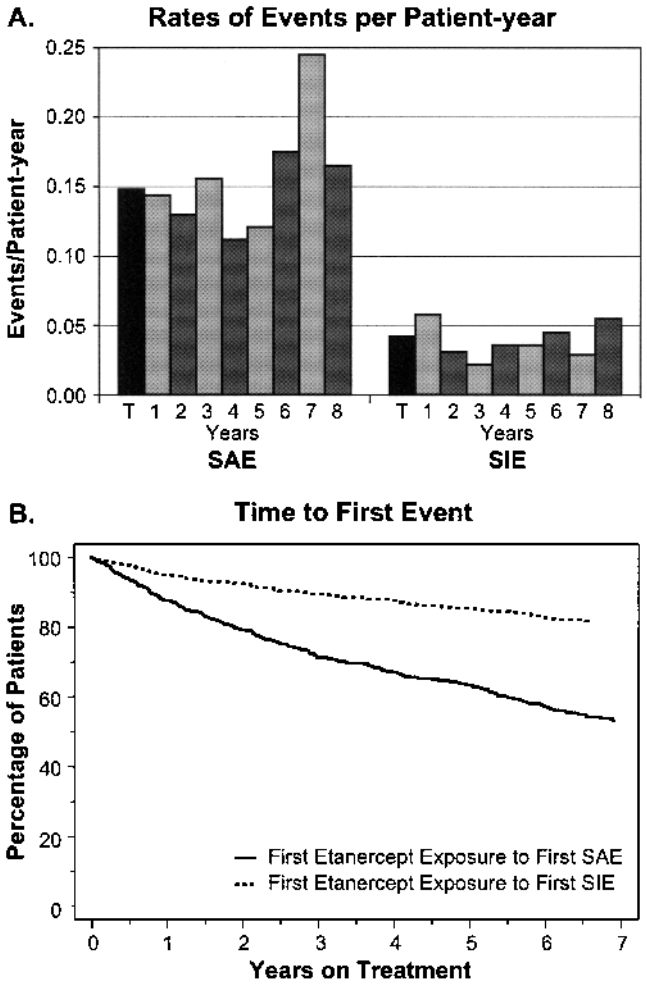

Figure 3. Serious adverse events (SAE) and serious infections (SIE) occurring on study or within 30 days of the last dose of etanercept. Serious infection was defined as an infection requiring hospitalization or intravenous antibiotics. A. Data from patients who completed 8 years of followup and are in the 9th year of safety data (n = 13) are not included. T = total number of events (black bars). Gray shading was used for legibility. B. Kaplan-Meier curve of serious adverse events and serious infections over time in the study.

arthritis (8 patients, 10 events, 0.3 events/100 patient-yrs). Six cases of sepsis and one observation of positive blood cultures were reported. The expected number of cases of sepsis was 13, calculated from data from the general population by Angus, *et al*[22]. No reports of *Mycobacterium tuberculosis*, histoplasmosis, or listeriosis were received.

Rates of infection have been reported for 2 cohorts of patients with RA. The Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) database is a prospectively defined cohort of 5569 RA patients with data on infections requiring hospitalization[23]. The Olmsted County cohort is a retrospectively defined, population-based, group of 609 RA patients[24]. The rate of serious infections observed in the ARAMIS cohort was 3.1 events/100 patient-years (26,419 patient-yrs); the rate observed in the Olmsted County cohort was 9.6 events (7730 patient-yrs).

Malignancies. Twenty-nine (4%) patients had 30 malignancies (not including non-melanoma skin cancers or *in situ* carcinomas) during the study or within 30 days of the last dose of etanercept (1.0 event/100 patient-yrs). One patient had recurrent ovarian cancer; the recurrent cancer was not counted as a second cancer. The patient with 2 primary malignancies had squamous cell carcinoma of the larynx at Day 787 of etanercept treatment and lymphoma on Day 1842 of etanercept treatment. The most common malignancies were lymphoma (n = 7; 2 Hodgkin's lymphomas and 5 non-Hodgkin's lymphomas), lung cancer (n = 5), ovarian cancer (n = 4), and breast cancer (n = 3). There were 2 cases each of leukemia, prostate cancer, and malignant melanoma. For the general population, the expected number of malignancies at all sites (excluding non-melanoma skin cancers or *in situ* carcinomas) was 28, and the expected number of lymphomas was 1, calculated using the Surveillance, Epidemiology, and End Results (SEER) database for age- and sex-matched cohorts[25].

Of the non-melanoma skin cancers not included above, 4 cases of squamous cell skin carcinomas and 11 cases of basal cell skin carcinomas were reported through the first year of the extension. Rates of non-melanoma skin cancers were not calculated beyond the first year of the extension since non-serious adverse events were not collected after this timepoint. Comparative data on the incidence of non-melanoma skin cancers are scarce; however, the expected number of squamous cell carcinomas, calculated using the Rochester Epidemiology Project data[26] from the general population, was 4. The expected number of basal cell carcinomas, calculated using the Southeastern Arizona Skin Cancer Registry data from the general population[27], was 8. The expected number of incident cases of basal cell carcinomas for an age- and sex-matched cohort from the general population was 34[27].

Deaths. Twenty-two deaths (3%) were reported among the 714 patients who received etanercept in either the initial clinical trials or the extension (0.7 deaths/100 patient-yrs), including 2 patients who died more than 30 days after receiving the last dose of etanercept. The most common reported causes of death were cardiac event (n = 9), malignancy (n = 3), and sepsis (n = 2; one was due to *Streptococcus pneumoniae* and the other was due to *Staphylococcus aureus*). The expected number of deaths in the general population was 35, calculated using the National Vital Statistics Report[28] and corrected for age and sex.

Efficacy of etanercept. ACR response rates were calculated per year, for all patients who completed that full year of therapy. The ACR20 response was 70% at Year 1 and ranged from 67% to 78% through 7 completed years of etanercept therapy (Table 2). Similarly, the ACR50 response at Year 1 was 44% and ranged from 44% to 53% over 7 years of therapy. Disease activity, as measured by DAS28 CRP, decreased from a mean (SD) of 6.1 (1.1) at baseline to 3.7 (1.3) at Year 1, and in subsequent years through Year 7, the mean values ranged from 3.2 to 3.4 (Table 2).

Additional indices of the magnitude of the clinical response and the proportion of patients achieving various levels of improvement were calculated. The proportions of patients achieving DAS28 CRP good responses, DAS28 CRP remission, and ACR70 responses were evaluated (Table 2). From Years 1 through 7, DAS28 CRP good responses ranged from 37% to 54%, and DAS28 CRP remission ranged from 23% to 37% of patients. Similarly, ACR70 responses ranged from 19% to 27%. As an estimate of the proportion of patients who achieved normal function, 13% to 17% of patients had a HAQ = 0 at Years 1 through 7 of etanercept therapy. A complete response occurred in 7% to 15% of patients, depending on the year of therapy that was completed. Using CRP as a serum measure of systemic inflammation, 48% to 65% of patients achieved a normal CRP at Years 1 to 7 of etanercept exposure (Table 2).

At baseline, the median number of tender/painful joints was 30.0 and of swollen joints 24.0 (Table 2). At Year 1, the median numbers of tender/painful and swollen joints both decreased to 6.0, and both remained at 6.0 or less from Years 2 through 7.

For physician and patient global assessment of disease activity, patient assessment of pain, General Health Score, HAQ feeling thermometer, and HAQ scores, similar patterns were seen (Table 2). The significant clinical improvements seen at Year 1 were consistently sustained through Year 7. The mean HAQ score decreased from 1.5 at baseline to 1.0 by Year 1. This clinically significant improvement in physical function was sustained from Years 1 to 7. By Year 1, 72% of patients achieved an improvement in HAQ of 0.22 compared with baseline. The proportion of patients who achieved a HAQ score of zero is shown is Table 2. The mean CRP level was 3.0 mg/dl at baseline, decreased to 0.8 mg/dl at 1 year, and was 0.4 mg/dl at Year 4. CRP levels remained stable from Years 4 through 7. The mean (SD) ESR was 38 (27) mm/h at baseline, decreased to 27 (22) mm/h at Year 1, and remained stable through Year 2.

Table 2. Composite scores and measures of significant improvement over time.

	Years Post-Baseline in the Extension								
	Baseline[a] (n = 644)[b]	Year 1 (n = 560)	Year 2 (n = 412)	Year 3 (n = 438)	Year 4 (n = 429)	Year 5 (n = 397)	Year 6 (n = 3560	Year 7 (n = 167)	Last Visit (n = 644)
ACR response, n (%)									
ACR20	NA	390 (70)	296 (72)	323 (74)	333 (78)	295 (74)	260 (73)	112 (67)	357 (55)
ACR50	NA	248 (44)	183 (44)	209 (48)	218 (51)	212 (53)	185 (52)	82 (49)	218 (34)
ACR70	NA	106 (19)	88 (21)	115 (26)	107 (25)	98 (25)	95 (27)	41 (25)	111 (17)
DAS28 CRP score, mean (SD)	6.1 (1.1)	3.7 (1.3)	3.5 (1.3)	3.4 (1.3)	3.4 (1.3)	3.2 (1.2)	3.2 (1.4)	3.3 (1.4)	4.1 (1.6)
Measures of significant improvement, n (%)									
DAS28 CRP = Good[c]	NA	201 (37)	171 (42)	207 (48)	196 (47)	198 (52)	178 (52)	64 (47)	147 (31)
DAS28 CRP remission[d]	NA	126 (23)	121 (30)	136 (32)	134 (32)	141 (37)	127 (37)	49 (36)	96 (20)
HAQ = 0	13 (2)	66 (13)	59 (15)	64 (15)	71 (17)	61 (15)	57 (16)	21 (13)	64 (10)
CRP = normal	132 (20)	262 (48)	219 (53)	255 (59)	265 (63)	249 (65)	219 (64)	77 (57)	210 (44)
Complete response[e]	NA	44 (8)	56 (14)	32 (7)	54 (13)	54 (14)	54 (15)	27 (16)	67 (10)
Other disease activity variables									
Tender joints, mean (SD)	31.3 (14.7)	9.7 (11.2)	9.0 (11.6)	8.0 (10.7)	8.7 (12.2)	7.2 (10.4)	7.9 (11.3)	8.6 (12.5)	11.4 (13.8)
Swollen joints, mean (SD)	24.5 (11.4)	9.3 (9.3)	7.2 (8.0)	7.2 (7.6)	7.3 (8.3)	6.1 (7.5)	6.1 (7.2)	5.5 (7.5)	9.2 (10.1)
Physician global assessment, mean (SD)[f]	6.6 (1.7)	2.9 (1.8)	2.7 (2.0)	2.5 (1.8)	2.5 (1.8)	2.5 (1.8)	2.5 (1.9)	2.6 (2.2)	3.4 (2.5)
Patient global assessment, mean (SD)[f]	6.6 (2.0)	3.2 (2.1)	3.3 (2.2)	3.2 (2.2)	3.4 (2.3)	3.3 (2.2)	3.5 (2.4)	3.5 (2.4)	4.1 (2.5)
Patient assessment of pain, mean (SD)[f]	5.9 (2.5)	2.6 (2.3)	2.7 (2.3)	2.6 (2.3)	2.8 (2.4)	2.7 (2.3)	3.0 (4.8)	3.4 (5.5)	4.3 (6.9)
General health VAS, mean (SD)[g]	56 (22)	28 (20)	29 (22)	30 (21)	31 (22)	29 (21)	30 (22)	32 (22)	39 (25)
HAQ feeling thermometer, mean (SD)[h]	53 (23)	77 (18)	77 (19)	76 (19)	76 (19)	77 (19)	76 (19)	74 (20)	69 (23)
HAQ, mean (SD)[i]	1.5 (0.7)	1.0 (0.7)	1.0 (0.7)	1.0 (0.8)	1.0 (0.7)	1.0 (0.7)	1.0 (0.7)	1.0 (0.8)	1.2 (0.8)
HAQ improvement ≥ 0.22, % patients		72	66	66	69	67	65	59	57

ACR: American College of Rheumatology; CRP: C-reactive protein; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire; NA: not applicable. [a] Efficacy timepoints are relative to baseline of the initial studies except for 8 patients who had an 18-month gap between the initial and extension studies. The timepoints for these 8 patients were relative to the baseline of the extension. All values are observed cases. [b] Patients treated with etanercept who had sufficient data to be included in the efficacy analyses. [c] DAS28 CRP Good: improvement from baseline of > 1.2 and achievement of disease activity < 3.2. [d] DAS28 CRP remission: DAS < 2.6. [e] Complete response: zero tender and swollen joints. [f] 0 = best, 10 = worst. [g] 0 = best, 100 = worst. [h] 0 = worst, 100 = best. [i] 0 = best, 3 = worst.

DISCUSSION

Results from extensive longterm experience with etanercept in patients with DMARD-refractory RA are presented. Most patients were female, with a mean age of 52 years and a mean of 12 years of active RA. Functional disability was significant at the time of entry (mean HAQ was 1.5).

Etanercept was generally well tolerated during longterm treatment. Exposure-adjusted rates of SAE and serious infections were comparable to those observed in the control- and etanercept-treatment groups of controlled trials. The rates and types of SAE and serious infections remained stable over time with increased exposure to etanercept. Similarly, the rates of cancer, deaths, and withdrawals due to adverse events remained stable with increased exposure to etanercept. No reports of tuberculosis, histoplasmosis, or listeriosis were received despite lack of ppd testing during enrollment. The number of cases of sepsis observed did not exceed the number expected.

The number of deaths observed in patients in the extension was numerically lower than the expected number of deaths for the general population, calculated based on data from the National Vital Statistics Reports and adjusted for age and sex[28]. Mortality rates did not increase with increased exposure to etanercept.

The rates of serious infections observed in the 714 patients throughout 8 years of exposure to etanercept were similar to rates observed in the ARAMIS and Olmsted County cohorts and similar to rates observed in RA patients in the controlled portions of the initial clinical trials, suggesting that rates of serious infections in patients with RA treated with etanercept are not different from rates for other patients with RA. However, patients from clinical trials may have fewer comorbidities than the patients in population-based registries and therefore might be expected to have fewer infections than patients in the ARAMIS and Olmsted County cohorts[23,24]. A systematic review is needed of the incidence of serious infections in patients with RA.

The rates of malignancies observed were within the range expected for the general population, with the exception of lymphoma. The expected numbers of squamous and basal cell skin carcinomas seen in the extension trial were not different from those calculated for age- and sex-matched cohorts from the general population using data from the Southeastern Arizona Skin Cancer Registry[27] and the Rochester Epidemiology Project[26]. Systematic reviews are needed of the incidence of cutaneous and noncutaneous malignancies in patients with RA.

In our report of longterm followup of patients with RA

receiving etanercept, 7 cases of lymphoma were observed compared with 1 lymphoma expected in the general population (calculated using the SEER database). Lymphoma and other hematopoietic tumors are known to occur at higher rates in patients with RA than in the general population[29-33], especially in patients with severe disease similar to those who enrolled in this extension trial. The standardized incidence ratio (SIR, observed/expected cases) for lymphoma in RA patients not receiving biologic therapy compared with patients from the general population has been variously estimated to be 1.9 or at least 2.2 based on data across multiple studies[34,35]. Using these estimates, the SIR for lymphoma for the patients in this extension study is 3.2–3.7 (7 cases/2.2; 7 cases/1.9) relative to the estimated expected rate in the RA population. The relationship between disease severity, RA medications, and lymphoma remains to be answered. However, a recent review of lymphoma in 18,572 patients with RA failed to establish a causal relationship between RA treatments (MTX and anti-TNF therapy) and the development of lymphoma[35].

Controlled trials have demonstrated the safety and efficacy of etanercept in patients with RA. Treatment with etanercept resulted in rapid clinical benefit without significant safety concerns. The efficacy and safety results of the controlled trials are reinforced by the longterm results presented in this report. Treatment with etanercept resulted in durable clinical responses for over 7 complete years of etanercept treatment in adults with established RA (the longest treatment duration at the time of this report was 8.2 years).

Many patients who were receiving concomitant MTX or corticosteroids were able to reduce their doses or discontinue these concomitant therapies during the extension. Since use of MTX and corticosteroids in the treatment of RA is associated with adverse events, and their use may be limited by toxicities, the ability to decrease or discontinue these medications confers flexibility in treatment options, which is a potential safety benefit to patients.

In conclusion, adult patients with RA treated with etanercept experienced rapid clinical improvement and durable clinical responses that were sustained for 7 years or more. In most patients that enrolled in the extension, there was sustained improvement in rheumatoid arthritis variables including functional status and acute phase reactants. In this selected population, etanercept was well tolerated with no increase in the rates of serious adverse events.

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