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ORIGINAL ARTICLE

Safety and Efficacy of Etanercept Beyond 10 Years of Therapy in North American Patients With Early and Longstanding Rheumatoid Arthritis

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Objective. **To evaluate the long-term safety and efficacy of etanercept therapy in rheumatoid arthritis (RA) patients.**
Methods. **Adult patients with early RA or longstanding RA received etanercept in open-label extension studies following initial double-blind trials of etanercept.**
Results. **Of 558 early RA patients and 714 longstanding RA patients who received at least 1 dose of etanercept, a total of 194 early RA patients and 217 longstanding RA patients were treated with 25 mg of etanercept twice weekly through 10 years. Five opportunistic infections were reported: in early RA, 1 *Candida* septicemia; in longstanding RA, 1 herpes zoster, 1 atypical mycobacterium infection, 1 meningoencephalitis (unspecified), and 1 fungal sepsis (unspecified). Twenty-nine cases of sepsis occurred (10 early RA, 19 longstanding RA). Occurrence of all malignancies was similar to that expected in the general population, but the occurrence of lymphomas was higher than expected in the general population. Fourteen lymphomas (7 early RA, 7 longstanding RA) and 2 cases of demyelinating disease (1 early RA, 1 longstanding RA) were reported. Deaths occurred in 18 early RA patients and 43 longstanding RA patients. Both patient groups showed sustained improvement in American College of Rheumatology responses, swollen joint counts, Health Assessment Questionnaire disability index scores, and C-reactive protein levels.**
Conclusion. **Etanercept maintained therapeutic benefits beyond 10 years of therapy in both early RA and longstanding RA patients, suggesting that etanercept is well tolerated and effective as a long-term, continuous therapy for the treatment of RA, with a favorable risk/benefit ratio.**

INTRODUCTION

Tumor necrosis factor (TNF) blockers have dramatically improved the treatment of rheumatoid arthritis (RA) over the past 10 years. With the increasingly widespread and prolonged use of these agents, assessments of their long-term safety and efficacy are extremely important. Several trials have reported the safety and efficacy of etanercept, a fully-human soluble receptor Fc fusion protein, in the treatment of patients with early RA (1,2) or moderate to

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severe longstanding RA (3–8). The primary objective of the extension studies was to evaluate the long-term safety of etanercept in patients with early RA and longstanding RA. The secondary objective was to describe the long-term effectiveness, demography, patient exposure, and study discontinuations of etanercept over time.

PATIENTS AND METHODS

RA patients ages ≥18 years who were randomized to either etanercept or methotrexate (MTX) therapy in 1 early RA parent study (1,2) and patients who received etanercept therapy in 1 or more of 8 different longstanding RA parent studies (4,5,8) were eligible to enroll in long-term, open-label extension studies at multiple centers throughout North America, during which they received etanercept 25 mg twice weekly administered as subcutaneous injections. Early RA patients received their disease diagnosis ≤3 years prior to initial enrollment and longstanding RA patients had less than an optimal response to ≥1 previous disease-modifying antirheumatic drugs (DMARDs). Patients who did not receive MTX in the parent studies were permitted to add MTX in the long-term extension studies if needed. The percentage of patients receiving oral corticosteroids at various time points was assessed.

The parent early RA study lasted 2 years, although patients were allowed to withdraw after 1 year and still participate in the long-term extension. Those who completed 2 years went directly into the long-term extension. The 8 different parent longstanding RA studies lasted 1 to 12 months; some patients participated in 1 to 3 longstanding RA studies before the long-term extension study was available. Unlike early RA, there were gaps between longstanding RA parent studies and before enrollment in the extension study.

This report includes data from the initial parent studies plus the long-term extension studies. Efficacy assessments were performed every 6 months from month 24 through month 144. For early RA, we report 12 years of safety and 12 years of efficacy, which include the single parent study (up to 2 years) plus the long-term extension study (up to 10 years). For longstanding RA, we report 15 years of safety and 11 years of efficacy, which include the 8 different parent studies (up to 4 years in total) plus the long-term extension study (up to 11 years). The final efficacy analysis includes patients who completed the study to closure, defined as those who had an office visit between June and December 2008 and/or completed an end-of-study form. These studies were conducted in accordance with the Good Clinical Practice guidelines provided by the International Conference on Harmonisation and are registered with ClinicalTrials.gov with the identifiers NCT00356590 (the early RA extension study) and NCT00357903 (the longstanding RA extension study). All of the patients gave written informed consent.

Safety assessments. Safety results are presented for all of the patients who received at least 1 dose of etanercept in either the long-term extension studies or their parent studies. Safety assessments focus on exposure to etanercept; safety-related discontinuations; serious adverse events (SAEs), including demyelination events, malignancies, and cardiovascular events; serious infectious events (SIEs), including sepsis; opportunistic infections (OIs); and deaths. The numbers of deaths and malignancies were compared to those expected based on age- and sex-matched cohorts from the general population (calculated using the Surveillance, Epidemiology, and End Results [SEER] database [1998–2002]) using total time receiving etanercept (in patient-years), including gaps between studies.

SAEs were defined as any adverse drug experience that resulted in death, was life-threatening, or required hospitalization (9), and were classified using a modified version of the Coding Symbols for a Thesaurus of Adverse Reaction Terms dictionary. SIEs were defined as all SAEs that occurred as the result of an infection. Exposure-adjusted rates of events per patient-year were calculated as the total number of events reported divided by total etanercept exposure (summed over patients), excluding time elapsed between studies. The definition of OI was based on that provided for patients with human immunodeficiency virus by the Centers for Disease Control and Prevention Wonder online database (1992) (10).

Efficacy assessments. In the early RA parent study, patients were randomized to receive 1 of 3 treatment regimens: etanercept 10 mg twice weekly (n = 208), etanercept 25 mg twice weekly (n = 207), or oral MTX with dose titration by week 8 to 20 mg/week if tolerated and necessary to reduce the number of tender/painful or swollen joints (n = 217). Early RA and longstanding RA patients were required to receive 25 mg twice weekly in the extension study. Efficacy results in early RA are presented only for patients who received etanercept 25 mg twice weekly in the parent study and extension study. Efficacy results in longstanding RA are presented only for patients who had at least 1 postbaseline efficacy measure later than 45 days after the first dose of etanercept in a longstanding RA parent study. Thirty-eight longstanding RA patients who had received etanercept 10 mg twice weekly in one of the parent studies were allowed to continue in the extension study on this dose if their arthritis was well controlled. Efficacy assessments included the American College of Rheumatology criteria for 20%/50%/70% improvement in disease activity (ACR20/50/70) responses (11), tender and swollen joint counts, Health Assessment Questionnaire disability index (HAQ DI) score, C-reactive protein (CRP) level, and remission based on the 28–joint count Disease Activity Score (DAS28).

CRP analysis. For ACR responses, CRP values using the enzyme immunoassay (EIA) of CRP are reported for results obtained prior to December 2004 (early RA: months 1–78, longstanding RA: months 1–60). After this date, implementation of the new high-sensitivity method of analyzing CRP became available. During implementation of the new methodology, CRP values from the EIA and high-sensitivity methods were treated as equivalents and averaged (early RA: months 84–90, longstanding RA: months 66–

Table 1. Baseline demographics*

	Received initial treatment†		Discontinuations‡	
	Early RA (n = 558)	Longstanding RA (n = 714)	Early RA (n = 364)	Longstanding RA (n = 497)
Women	75	79	74	78
White	86	90	83	91
Age, years				
Mean	50	53	51	54
Range	19–84	18–86	19–84	18–86
Duration of RA, mean years	0.8	12.1	0.8	12.4
Rheumatoid factor positive	88	70	88	68
Prior DMARDs, mean	0.5	3.4	0.6	3.4
Concomitant therapy				
Corticosteroids	40	45	42	47
NSAIDs	81	50	79	50

* Values are the percentage unless otherwise indicated. RA = rheumatoid arthritis; DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal antiinflammatory drugs.
† Number of patients who received at least 1 dose of etanercept in either the parent or long-term study.
‡ Number of patients who discontinued either the parent or long-term study before completion.

90). CRP values using the high-sensitivity method were reported only from ≥96 months for the cumulative data set.

Statistical analysis. Etanercept exposure over time was characterized by dosing period and was summarized descriptively. Specific dosing information was not collected after year 1 of the extension studies. Patient exposure to etanercept was calculated for each year based on patients receiving ≥1 dose of etanercept during that interval and was calculated under the assumption that patients received etanercept 25 mg twice weekly until the last date of assessment or discontinuation. The proportion of patients continuing on etanercept was calculated using Kaplan-Meier estimates. No imputation or estimation methods were used for missing values during the study; efficacy data are based on all available data at each time point (observed data only). If joints were unevaluable at baseline due to being replaced or fused, the joint count was prorated from baseline onward; if joints were unevaluable postbaseline, they were not prorated.

Safety events occurring ≤30 days after the last dose were analyzed. All deaths and OIs, regardless of the 30-day window, are reported. Malignancies were identified from reported adverse events (AEs) and SAEs. AEs and SAEs were reported during the randomized controlled studies and the first 12 months of the open-label extensions; after 12 months, only SAEs were reported. Malignancies occurring ≤30 days from the last dose were used in the calculation of the standardized incidence ratio (SIR); malignancies reported >30 days after the last dose are noted. The SIRs for malignancies and lymphomas were calculated as the observed number of cases divided by the expected number of cases; a corresponding 95% confidence interval (95% CI) was calculated by the exact method based on the Poisson distribution. Reported malignancies excluded nonmelanoma skin cancers, in situ carcinomas, and cases of recurrent cancers. Only SAE malignancies were required to be collected during the extension studies.

RESULTS

A total of 632 patients were enrolled in the early RA parent study (415 etanercept patients and 217 MTX patients). Of these, 468 patients continued in the extension study and received etanercept 25 mg twice weekly. Five hundred eighty-one longstanding RA patients entered the extension study. A total of 558 early RA patients (415 original etanercept patients plus 143 of the 217 original MTX patients) and 714 longstanding RA patients received at least 1 dose of etanercept in either the parent or long-term extension study and were included in the safety analysis. Schemas illustrating the disposition of early RA patients and longstanding RA patients are shown in Supplementary Appendices A and B, respectively (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

Although baseline demographics were different between early RA and longstanding RA patients (specifically in regard to RA duration and prior DMARD use), they were comparable between early RA and longstanding RA patients who received at least 1 dose of etanercept in either the parent or long-term study, as well as those who discontinued any of the studies; the majority of patients were women, white, and rheumatoid factor positive (Table 1). A total of 163 (29%) of 558 early RA patients and 264 (37%) of 714 longstanding RA patients were followed through year 10 (Table 2). The median duration of etanercept exposure was 7.2 years (3,590 total patient-years) for early RA patients and 6.3 years (4,594 total patient-years) for longstanding RA patients.

During the exposure period (parent or long-term extension), a total of 364 (65%) of 558 early RA patients and 497 (70%) of 714 longstanding RA patients discontinued, and 194 (35%) of 558 early RA patients and 217 (30%) of 714 longstanding RA patients completed the extension study. The most common reasons for study discontinuation in early RA/longstanding RA were adverse events

Table 2. Duration of etanercept exposure*

	Early RA (n = 558)	Longstanding RA (n = 714)
Total patient-years of etanercept exposure	3,590.36	4,593.84
Median duration of exposure, years	7.2	6.3
No. of patients entering each year of the study†		
Year 1	558	714
Year 2	484	577
Year 3	439	519
Year 4	401	472
Year 5	372	440
Year 6	337	398
Year 7	301	364
Year 8	282	339
Year 9	265	321
Year 10	216	295
Year 11	163	264
Year 12	69	186
Year 13	N/A	42
Year 14	N/A	36
Year 15	N/A	9

* RA = rheumatoid arthritis; N/A = not applicable.
† Numbers indicate patients who have had followup assessments but who did not necessarily receive etanercept therapy.

(21%/22%), patient decision (16%/15%), and lack of efficacy (13%/21%) (Table 3).

Safety results. All of the patients who received at least 1 dose of etanercept in their extension study or parent study were analyzed for safety. As of the closing dates for these studies (early RA: December 12, 2008; longstanding RA: December 10, 2008), 194 early RA patients and 217 longstanding RA patients had been treated with etanercept 25 mg twice weekly through 10 years.

Exposure-adjusted rates of SAEs in both early RA and longstanding RA patients are shown in Table 4. The exposure-adjusted rate of SAEs per 100 patient-years was 12.1 for early RA patients and 18.4 for longstanding RA patients. The most common SAEs in early RA patients were pneumonia (4%; 22 patients), myocardial infarction (3%; 16 patients), aggravated reaction, i.e., worsening of disease or disease flares (2%; 13 patients), and spontaneous bone fracture (2%; 12 patients); the most common SAEs in longstanding RA patients were pneumonia (5%; 38 patients), worsening of RA symptoms (4%; 28 patients), spontaneous bone fracture (4%; 28 patients), aggravated reaction (4%; 25 patients), and myocardial infarction (3%; 24 patients).

Exposure-adjusted rates of SIEs in both early RA and longstanding RA patients remained relatively constant over time with continued exposure to etanercept (Table 5). The exposure-adjusted rate of SIEs per 100 patient-years was 2.6 for early RA patients (0.026 event/patient-year) and 4.4 for longstanding RA patients (0.044 event/patient-year). The most common SIEs in early RA patients were pneumonia (4%; 22 patients), cholecystitis (1%; 8 patients), and cellulitis, infection, sepsis, and bronchitis (1% each; 7 patients each); the most common SIEs in longstanding RA patients were pneumonia (5%; 38 patients), cellulitis (3%; 24 patients), infection (3%; 20 patients), and sepsis (2%; 16 patients). No cases of tuberculosis were observed. An OI of *Candida* septicemia was reported in 1 early RA patient who was hospitalized with pneumococcal pneumonia, sepsis, and respiratory failure; 1 month later, bronchial lavage showed *Candida*.

Four infections considered OIs were reported in longstanding RA patients: 1 herpes zoster, 1 atypical mycobacterium infection, 1 meningoencephalitis (unspecified) >30 days past the last dose date, and 1 fungal sepsis (unspecified) >30 days past the last dose date. All of the patients with OIs were discontinued from the study. Ten cases of sepsis were reported in early RA patients (none fatal) and 19 cases of sepsis were reported in longstanding RA patients (4 fatal). Although the risk of sepsis is higher in the RA population, the number of sepsis cases observed was lower than the expected number (14.3) for early RA patients and similar to the expected number (20.5) for longstanding RA patients, based on the general population (adjusted for age and sex) (12).

Serious malignancies (e.g., leukemias, lymphomas, myelomas, melanomas, solid tumors) were defined as all SAEs that were malignancies. Rates of overall serious malignancies for early RA and longstanding RA patients (0.01 event per patient-year for both) were relatively constant over 10 years with increasing continued exposure to etanercept. Early RA rates ranged from a yearly low of 0.002 to a yearly high of 0.022 per patient-year over the study period; longstanding RA rates ranged from a yearly low of 0.005 to a yearly high of 0.022 per patient-year. Thirty-

Table 3. Discontinuations during the exposure period*

	Early RA (n = 364)	Longstanding RA (n = 497)
Adverse events	78 (21)	110 (22)
Patient decision†	60 (16)	73 (15)
Lack of efficacy/disease exacerbation	47 (13)	102 (21)
Physician decision‡	46 (13)	39 (8)
Lost to followup	40 (11)	25 (5)
Protocol issues	14 (4)	18 (4)
Death	10 (3)	34 (7)
Other§	57 (16)	52 (10)
Completed parent study but did not enroll in extension study	10 (3)	44 (9)
Completed month 12 only of parent study	2 (1)	N/A

* Values are the number (percentage). RA = rheumatoid arthritis; N/A = not applicable.
† Patient decisions encompassed a variety of reasons, e.g., withdrawal of consent, complete remission, and refusal to continue.
‡ Physician decisions encompassed noncompliance, possible immunosuppression, and switching treatment regimen.
§ There also was a wide range of "other" discontinuation reasons, including patient moved, pregnancy, site closure, unable to self-inject, etc.

Table 4. Serious adverse events*

	Controlled trials		Long-term etanercept therapy										
	Placebo or MTX	Etanercept	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	Yr 6	Yr 7	Yr 8	Yr 9	Yr 10	Overall
Event rates (per patient-year)													
Early RA	0.11	0.09	0.10	0.08	0.08	0.10	0.15	0.16	0.13	0.18	0.12	0.19	0.12
Longstanding RA	0.20	0.15	0.11	0.10	0.14	0.14	0.15	0.17	0.24	0.28	0.30	0.27	0.18

* MTX = methotrexate; RA = rheumatoid arthritis.

three early RA patients reported 39 serious malignancies during 3,590 patient-years of therapy, and 48 longstanding RA patients reported 60 malignancies during 4,594 patient-years of therapy. The most common serious malignancies reported in early RA were lymphoma (1.5%; n = 7), prostate and lung carcinoma (each 1.1%; n = 6), and breast carcinoma (0.9%; n = 5). The most common serious malignancies reported in longstanding RA were unspecified carcinomas and lung cancer (each 1.1%; n = 8), lymphoma (1.0%; n = 7), and prostate, breast, and gastrointestinal carcinoma (each 0.8%; n = 6).

To compare results with the general population, malignancy incidences reported during the study were compared with expected incidences for those in an age- and sex-matched cohort from the SEER database (1998–2002). Using the SEER parameters (which exclude nonmelanoma skin cancers, in situ carcinomas [except bladder in situ carcinomas], and recurrent cancers), 30 malignancies were observed for early RA patients compared with 30.2 malignancies expected for the general population; 52 malignancies were observed for longstanding RA patients compared with 43.6 malignancies expected for the general population (Table 6). The SIRs (observed/expected) were 0.99 with a 95% CI of 0.67–1.42 for early RA patients and 1.19 (95% CI 0.89–1.56) for longstanding RA patients.

In addition, a total of 14 lymphomas (7 in each study) were reported; compared to the SEER database, these incidences were higher than expected (early RA: 1.2, longstanding RA: 1.7). The SIRs (observed/expected) were 5.8 (95% CI 2.33–11.94) for early RA and 4.1 (95% CI 1.63–8.37) for longstanding RA. A total of 3 leukemias were reported <30 days after the last dose: 1 lymphocytic leukemia (early RA) and 1 lymphocytic leukemia and 1 myeloid leukemia (longstanding RA). In addition, 1 case of lymphocytic leukemia was reported >30 days after the last dose in early RA. The SIRs were 1.7 (95% CI 0.04–9.49) for early RA patients and 2.4 (95% CI 0.29–8.70) for longstanding RA patients.

Demyelinating disease was reported in 1 early RA patient in year 6 and in 1 longstanding RA patient in year 2; both patients had an abnormal brain magnetic resonance image and were discontinued from the study. The early RA patient had a questionable history of multiple sclerosis and experienced headaches and visual disturbances associated with demyelinating disease after 10 months of etanercept therapy. The longstanding RA patient experienced lower trunk and lower extremity sensory and spasticity changes after 15 months of etanercept therapy and was diagnosed with multiple sclerosis.

There were 38 (6.8%) of 558 early RA patients and 63 (8.8%) of 714 longstanding RA patients who had a cardiovascular event, the most frequent being myocardial infarction (n = 16 [2.9%] early RA, n = 24 [3.4%] longstanding RA). Additional cardiovascular events occurring in greater than 1% of patients included cerebrovascular accident (n = 8 [1.4%]), angina pectoris (n = 7 [1.3%]), and coronary artery disease (n = 6 [1.1%]) in early RA patients and coronary artery disease (n = 14 [2.0%]), heart failure (n = 13 [1.8%]), and cerebrovascular accident (n = 8 [1.1%]) in longstanding RA patients.

Rates of death did not increase over time with increasing exposure to etanercept. Among the 558 early RA patients, 18 deaths were reported (including 4 patients who died >30 days after the last dose of etanercept). Among the 714 longstanding RA patients, 43 deaths were reported (including 12 patients who died >30 days after the last dose of etanercept). Death rates observed in the long-term studies were compared with expected death rates for the gen-

Table 5. Serious infectious events*

	Controlled trials†		Long-term etanercept therapy‡										
	Placebo or MTX	Etanercept	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5	Yr 6	Yr 7	Yr 8	Yr 9	Yr 10	Overall
Event rates (per patient-year)													
Early RA	0.03	0.02	0.03	0.02	0.02	0.03	0.04	0.03	0.02	0.04	0.02	0.05	0.03
Longstanding RA	0.05	0.04	0.04	0.03	0.04	0.04	0.04	0.04	0.04	0.05	0.06	0.05	0.04

* MTX = methotrexate; RA = rheumatoid arthritis.
† Event rates based on the definition of medically-important infections (infections associated with hospitalization or intravenous antibiotics).
‡ Event rates based on the current definition of serious infectious events (serious adverse events that were infectious).

Table 6. Malignancies and deaths

	Malignancies		Deaths	
	Early RA (n = 468)	Longstanding RA (n = 714)	Early RA*	Longstanding RA
All cancers				
Expected†	30	44		
Observed‡	30	52		
Lymphomas				
Expected†	1.2	1.7		
Observed§	7	7		
Leukemia				
Expected†	0.6	0.8		
Observed§	1	2		
Deaths (all causes)				
Expected¶			40	56
Observed#			18	43

* Includes all patients in the long-term extension study and excludes patients in the parent early rheumatoid arthritis (RA) study who did not continue in the extension study.
† Calculated using Surveillance, Epidemiology, and End Results (SEER; 1998–2002) data, age- and sex-matched for the general population.
‡ Observed on study or within 30 days after the last etanercept dose. Excludes nonmelanoma skin cancers, in situ carcinomas, and recurrent cancers, which are not included in the SEER (1998–2002) database.
§ Observed on study or within 30 days after the last etanercept dose.
¶ Calculated using the National Vital Statistics report (12), age- and sex-matched for the general population.
# All deaths are reported, including those >30 days past the last dose.

eral population (adjusted for age and sex) (13), which were calculated using 3,515 total patient-years for early RA and 4,594 total patient-years for longstanding RA patients, including gaps between studies. The total number of deaths reported for all of the patients was less than the number expected to occur in an age- and sex-matched cohort from

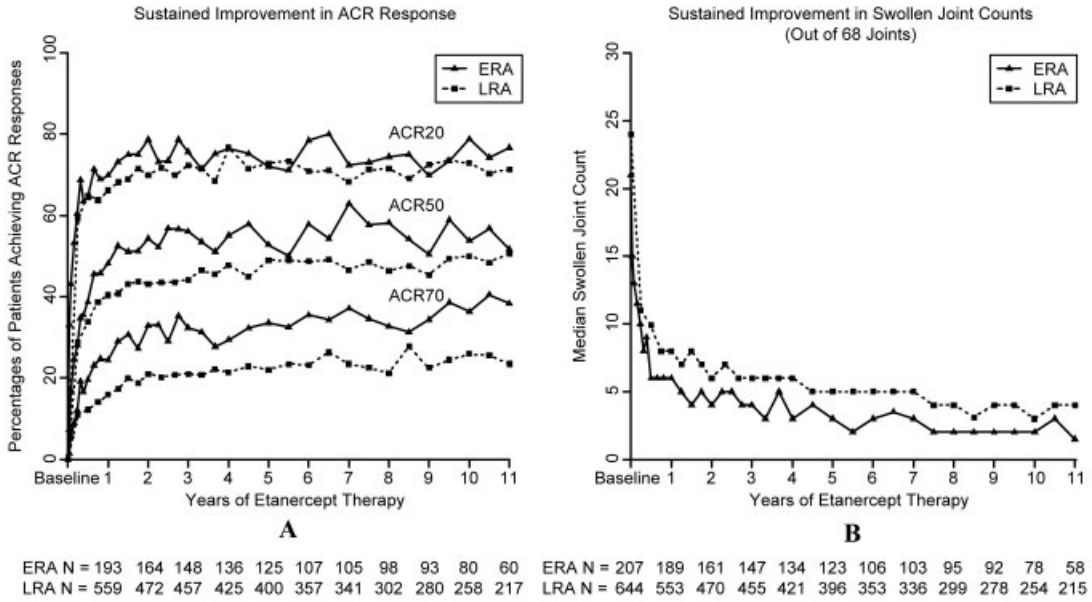

Figure 1. A, Sustained improvement in American College of Rheumatology (ACR) response. Percentages of early rheumatoid arthritis (ERA) patients and longstanding RA (LRA) patients who achieved ACR criteria for 20%/50%/70% improvement in disease activity (ACR20/50/70) responses from baseline throughout year 11 are shown. ACR data are reported using C-reactive protein (CRP) values based on the enzyme immunoassay (EIA) of CRP (ERA: months 1–78, LRA: months 1–60), the average of the EIA and the new high-sensitivity method (ERA: months 84–90, LRA: months 66–90), and the high-sensitivity method (ERA and LRA: months ≥96). Numbers of ERA and LRA patients evaluated during each year are indicated. Values were not available for all patients at all time points. **B,** Sustained improvement in swollen joint counts (of 68 joints). Median swollen joint counts for ERA patients and LRA patients from baseline throughout year 11 are shown. Numbers of ERA and LRA patients evaluated during each year are indicated. Values were not available for all patients at all time points.

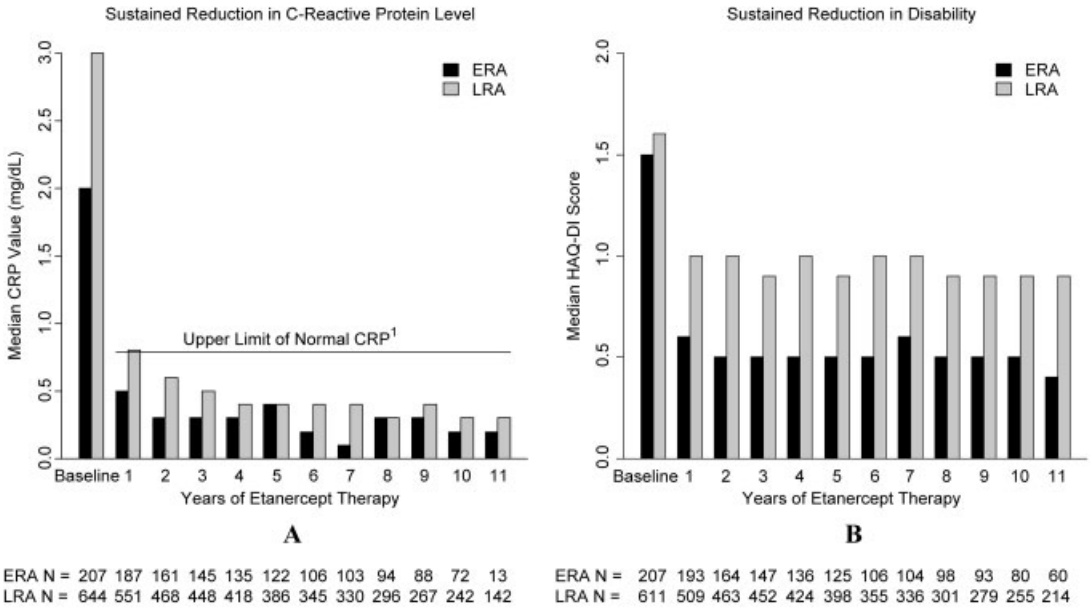

Figure 2. A, Sustained reduction in C-reactive protein (CRP) level. Median CRP values in mg/dl for early rheumatoid arthritis (ERA) patients and longstanding RA (LRA) patients from baseline throughout year 11 are shown. Numbers of ERA and LRA patients evaluated during each year are indicated. Values were not available for all patients at all time points. [1] = the upper limit of normal CRP was 0.79 mg/dl, using the enzyme immunoassay method. **B,** Sustained reduction in disability. Median Health Assessment Questionnaire disability index (HAQ-DI) scores for ERA patients and LRA patients from baseline throughout year 11 are shown. A lower HAQ-DI score indicates better functional ability (score range: 0 = best to 3 = worst). Numbers of ERA and LRA patients evaluated during each year are indicated. Values were not available for all patients at all time points.

the general population (18 versus 40 for early RA patients, 43 versus 56 for longstanding RA patients). The most common cause of death was cardiovascular. The overall distribution of causes of death was similar to a population-based cohort of patients with RA (14).

Efficacy results. Efficacy was analyzed for patients who initiated etanercept in their parent study and continued etanercept 25 mg twice weekly throughout the extension study. These included 207 of the 558 early RA patients and 644 of the 714 longstanding RA patients. After 10 years of open-label etanercept treatment, a completer analysis of improvements in ACR20, ACR50, and ACR70 responses showed that improvements were maintained in both groups; however, as would be expected, ACR50 and ACR70 responses were not as robust in longstanding RA patients compared with early RA patients (Figure 1A). There was sustained improvement in median swollen joints through the 10-year period (Figure 1B). At year 10, 42% of early RA patients and 29% of longstanding RA patients achieved a DAS28 remission (defined as a DAS28-CRP <2.6). The reported early RA yearly low for DAS28 remission was 28% and the yearly high was 48%; the reported longstanding RA yearly low was 18% and the yearly high was 33%. Sustained reductions in CRP levels are shown in Figure 2A. Greater median reductions in HAQ DI scores occurred in early RA patients compared with longstanding RA patients, also as expected, but HAQ DI reductions in both groups were clinically significant and sustained at each observation point through 10 years (Figure 2B); 24% to 33% of early RA patients and 13% to 20% of longstanding RA patients achieved a HAQ DI score of 0 at any given yearly assessment during the 10-year period.

Results of efficacy measures for study completers were compared to the results of patients who discontinued for any reason before study completion. ACR20/50/70 responses for patients at year 11 as shown in Figure 1A were 77%, 52%, and 38%, respectively, for early RA patients (n = 60) and 71%, 51%, and 24%, respectively, for longstanding RA patients (n = 217). For patients who discontinued prior to study completion, ACR20/50/70 responses were 50%, 33%, and 20%, respectively, for early RA patients (n = 364) and 39%, 20%, and 8%, respectively, for longstanding RA patients (n = 427) at their last visit. Among completers, median HAQ DI responses at year 11 were 0.4 (range 0–2.4) for the 60 early RA patients and 0.9 (range 0–2.9) for the 214 longstanding RA patients. For patients who discontinued prior to study completion, median HAQ DI scores were 1.0 (range 0–2.8) for early RA patients (n = 362) and 1.4 (range 0–3.0) for longstanding RA patients (n = 408) at their last visit. At year 11, mean ± SD DAS28-CRP values were 2.9 ± 1.0 for early RA patients (n = 12) and 3.3 ± 1.3 for longstanding RA patients (n = 136); other patients who completed the study were missing CRP values or did not have all of the components for the DAS28. In patients not completing the study to closure, the mean ± SD DAS28-CRP values were 4.0 ± 1.6 for early RA patients (n = 364) and 4.6 ± 1.6 for longstanding RA patients (n = 412) at their last visit. DAS28 remission (as defined above) at year 11 was achieved by 50% of early RA patients (n = 12) and 35% of longstanding RA patients (n = 136). DAS28-CRP <2.6 for patients who did not complete the study to closure for any reason was achieved

by 26% of early RA patients (n = 364) and 12% of longstanding RA patients (n = 412) at their last visit.

At baseline, 223 (40%) of 558 early RA patients and 318 (45%) of 714 longstanding RA patients were taking concomitant oral corticosteroids. A significant number of early RA patients discontinued steroids compared to patients in the longstanding RA study who did not. Of the 50 early RA patients who were taking corticosteroids at their last visit, 15 (13%) of 120 continued their baseline dose, 8 (7%) of 120 increased their baseline dose, 27 (23%) of 120 decreased their baseline dose, and an additional 70 (58%) of 120 patients discontinued corticosteroids. A total of 86 (72%) of 120 early RA patients had discontinued corticosteroids or decreased their dose by more than 50% of their baseline dose at the time of their last visit. A total of 50 (15%) of 324 early RA patients and 266 (46%) of 578 longstanding RA patients completed the study to closure on oral corticosteroids, compared with 36 (20%) of 182 early RA patients and 185 (51%) of 361 longstanding RA patients who were taking corticosteroids at their last visit but who did not complete the study to closure.

DISCUSSION

In summary, of the 558 early RA and 714 longstanding RA patients who received at least 1 dose of etanercept in these studies, a total of 194 early RA patients and 217 longstanding RA patients were treated with etanercept 25 mg twice weekly through 10 years. There were 364 and 497 study discontinuations for early RA and longstanding RA patients, respectively. Of these, 13% (47 of 364) of the study discontinuations for early RA patients and 21% (102 of 497) of the study discontinuations for longstanding RA patients were due to lack of efficacy or disease exacerbation. Twenty-one percent (78 of 364) of early RA study discontinuations and 22% (110 of 497) of longstanding RA study discontinuations were due to an AE.

In adult patients with early RA and longstanding RA, the safety profile of etanercept remained favorable with continuous etanercept therapy. Although rates of SIEs remained relatively constant over time with increasing exposure to etanercept, exposure-adjusted rates of SAEs increased with increasing etanercept exposure, possibly due to the effect of the drug itself or perhaps due to cumulative morbidities in an aging population. Rates of death were lower than expected compared with the general population.

The exposure-adjusted rates of SIEs (0.03 event/patient-year for early RA patients and 0.04 event/patient-year for longstanding RA patients) are similar to the rates observed in the Olmsted County, Minnesota, RA cohort (0.10 event/patient-year) (15) and the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) RA cohort (0.03 event/patient-year) (16). Also, rates of serious infections in the long-term etanercept database were similar to the control and etanercept groups of controlled phases of the studies. Therefore, RA patients in the Olmsted County and ARAMIS databases who were receiving traditional DMARD therapy had exposure-adjusted rates of SIEs similar to the patients in this study, who were taking biologic therapy with etanercept. Although active tuberculosis, including reactivation of latent tuberculosis, has been associated with the use of etanercept as well as other TNF blockers, there were no tuberculosis cases observed in this study. It is not known if the higher than expected lymphoma rate is related to TNF antagonism or whether it reflects the elevated lymphoma risk associated with RA, which is at least twice that of the general population (17,18), and may be higher in patients with higher disease activity (19).

This is the longest prospective study of anti-TNF therapy to date with some patients receiving more than 10 years of treatment. Since it is expected that patients with sufficient clinical and functional improvement and good tolerability would be most likely to continue in the study, this type of analysis will almost always demonstrate sustained safety and efficacy, and we report sustained improvement in multiple measures of clinical and functional efficacy through 10 years of etanercept therapy. Additionally, not all patients who discontinued the studies prior to completion did so for lack of efficacy; many of them had significant ACR20/50/70 responses, DAS28 scores, and HAQ DI improvement. Greater median reduction in the HAQ DI occurred in early RA patients compared with longstanding RA patients. The same observation has been previously noted in patients with recent RA (mean duration 1 year) compared with established RA patients (mean duration 12 years); HAQ scores decreased rapidly in all RA patients treated with etanercept, but the magnitude of the improvement was greater with early disease compared with established RA (20).

Reasons for study discontinuation proved to be similar between early RA and longstanding RA patients, a result that would not have necessarily been predicted because it would be expected that patients with longstanding RA would be older, have more active disease, and develop more comorbidities. In the early RA population, a reduction in corticosteroid dose and use was demonstrated; this was not seen in the longstanding RA population.

These studies have certain limitations. Even though no tuberculosis cases were observed in this study, active tuberculosis (including reactivation of latent tuberculosis) has been associated with the use of etanercept as well as other TNF blockers, as previously mentioned. A larger database of the Adverse Event Reporting System of the US Food and Drug Administration revealed that, from January 1998 to September 2002, a total of 113,000 patients had received etanercept therapy and the rate of occurrence of tuberculosis was approximately 35 per 100,000 etanercept-treated patients (21). Our smaller numbers of patients may be considered a study limitation when assessing the risk of tuberculosis. Also, patients in these studies were not analyzed according to history of malignancy, and a recent report suggests that the risk of developing melanoma may be higher in patients with a history of malignancy who undergo anti-TNF therapy (22).

An analysis of studies that span 10 years includes only patients who have sustained efficacy without the development of a significant AE that would cause the patient to exit the study prior to closure. Therefore, the efficacy analysis is restricted to patients who continue to maintain

improvement and, as with any completer analysis of efficacy, the results reported are generally positive (and may be better than the original study, depending on the method of analysis). Furthermore, long-term favorable outcomes may also be due in part to strict study exclusion criteria and stringent initial screenings of clinical trial patients. Clinicians should generally keep in mind that clinical trial patients may not be representative of the entire patient population. Also, the majority of patients in this study were white women, a demographic that may not be reflected in certain practice settings.

Another limitation specific to this analysis is that averaging the results of the CRP and high-sensitivity CRP assays could be problematic; however, averaging these 2 methods was the only way to be able to continue calculating the DAS28 and ACR scores over such a long time period. We acknowledge this technique as a potential weakness of the analysis. Nevertheless, the high-sensitivity method did not appear to affect ACR results according to Figure 1A, where data at years 8 to 10 represent the ACR response calculated using the high-sensitivity method of CRP analysis in comparison to baseline CRP scores calculated using the EIA method.

These data suggest that etanercept is safe and effective as a long-term, continuous therapy for the treatment of both early RA and longstanding RA patients, and the risk/benefit ratio of continuous long-term etanercept treatment of RA patients remains favorable.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Weinblatt had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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