Longterm Safety, Efficacy, and Radiographic Outcome with Etanercept Treatment in Patients with Early Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate safety, efficacy, and radiographic progression in patients with early rheumatoid arthritis (RA) undergoing longterm treatment with etanercept.

Methods. Patients with early RA (disease duration of 3 years or less) who had completed a 2-year efficacy study comparing etanercept and methotrexate (MTX) were followed in an extension where they received 25 mg etanercept twice weekly. Safety was summarized descriptively and compared with data from the efficacy study. Efficacy and radiographic progression were assessed using American College of Rheumatology response criteria, disease activity scores, and Total Sharp Score (TSS).

Results. Rates of serious adverse events and serious infections did not increase with longterm exposure to etanercept, and were similar to rates reported for the blinded portion of the efficacy study. Efficacy was sustained in patients who completed 5 years of etanercept treatment at the time of this report (N = 201), even in those who decreased or discontinued use of MTX or corticosteroids. No radiographic progression (change in TSS ≤ 0) was seen in 55% of patients with 5-year radiographs; negative change (TSS < 0) was seen in 11%.

Conclusion. Etanercept treatment in patients with early RA was generally well tolerated for up to 5 years. The results indicate sustained efficacy and decreased rate of radiographic progression. The rate of radiographic progression was low compared with other studies, emphasizing the benefit gained in patients with early aggressive RA who undergo longterm treatment with etanercept. (J Rheumatol 2005;32:1232–42)

Key Indexing Terms:
BIOLOGICAL RESPONSE MODIFIERS RHEUMATOID ARTHRITIS
CLINICAL TRIALS ETANERCEPT TREATMENT

In patients with rheumatoid arthritis (RA) the proinflammatory cytokine tumor necrosis factor (TNF) plays a major role in promoting the synovial inflammatory process, which can lead to progressive destruction of cartilage and bone[1]. Recent approaches to treatment of RA using biological therapies aimed at reducing biologically active TNF have been successful. Anti-TNF therapies have been shown to reduce signs and symptoms of RA and decrease the rate of progression of radiographic damage to joints[2-5].

Etanercept is a fully human, soluble, p75 TNF receptor fusion protein that binds and neutralizes TNF and lymphotoxin-α. Treatment with etanercept has been shown to slow the rate of radiographic damage when given as monotherapy, and this effect is more pronounced when etanercept is given in combination with methotrexate (MTX)[2,3].

Studies of etanercept monotherapy in patients with early RA have shown rapid onset of significant clinical improvements that are sustained for up to 2 years[2,6]. In this cohort of patients, treatment with etanercept monotherapy led to less progression of radiographic damage [as measured by Total Sharp Score (TSS)] after 2 years of treatment compared with MTX. Not only did treatment with etanercept slow the rate of radiographic progression, but it also halted progression in a majority of patients, and it was more effective in this regard than treatment with MTX alone[6].

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This cohort of patients with early RA is being followed in an open-label extension. The objective of this analysis is to evaluate safety, efficacy, and radiographic progression in early RA patients treated with etanercept for 5 years.

MATERIALS AND METHODS

Adult patients who had RA for not more than 3 years and had not been treated with MTX were eligible for enrollment in a randomized efficacy study in which treatment was double-blind until all patients had completed one year and open-label (with the originally assigned medication) for up to 2 years of treatment. Patients had at least 10 swollen and 12 tender joints, and were seropositive for rheumatoid factor (RF) or had at least 3 bone erosions on radiographs of hands, wrists, and feet (additional details of the inclusion criteria have been published[2]). Patients were randomly assigned to one of 3 treatment groups and received either rapidly dose-escalated MTX (up to 20 mg/week) or etanercept (Enbrel®) at a dose of 10 mg or 25 mg twice weekly by subcutaneous injection. Placebo tablets and injections were used to maintain blinding.

Patients who completed 2 years of treatment in the efficacy study were eligible for enrollment into an open-label longterm extension in which they received etanercept 25 mg twice weekly by subcutaneous injection (patients in the MTX group received both MTX and etanercept at the beginning of the extension). Patients were also enrolled in the extension if they had completed at least one year in the efficacy study, but had discontinued because of lack of efficacy or an adverse event unrelated to etanercept. During the interval between withdrawal from the double-blind phase of the efficacy study and enrollment into the extension, treatment with alternative (non-MTX) disease modifying antirheumatic drugs (DMARD) was permitted. However, a 2 week washout of all DMARD except MTX was required before enrollment into the extension. Patients starting etanercept in the extension were not permitted to alter RA medications for the first 3 months of treatment. Once this requirement was met, tapering of nonsteroidal antiinflammatory drugs (NSAID), MTX, and corticosteroids was permitted during the extension. Dose reductions had to be performed one medication at a time and the dose of a tapered medication was to be increased if the patient's disease activity worsened as a result of the taper (i.e., RA flare). At the investigator's discretion, MTX or prednisone could be started and the doses of these medications could be increased, if necessary.

Safety summaries include data from all patients who received at least one dose of etanercept. Reports of non-serious adverse events were collected during the efficacy study and for the first year of the extension, but not thereafter. Serious adverse events (SAE) were collected throughout the efficacy study and the extension. SAE were defined as events that were fatal or life-threatening, resulted in permanent or significant disability or incapacity, or were a congenital anomaly or birth defect, or those that required or prolonged an inpatient hospitalization. Serious infections were defined as infections requiring hospitalization or intravenous antibiotics.

Efficacy was assessed using the American College of Rheumatology (ACR) response criteria[7] and disease activity scores (DAS)[8] and included patient visits through December 31, 2002. DAS were calculated using C-reactive protein (CRP) instead of erythrocyte sedimentation rate (ESR)[9] and were based on evaluation of 28 joints, referred to here as DAS28 CRP. 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 subsequent assessments. Additional analyses included CRP and Health Assessment Questionnaire (HAQ).

Radiographic progression was assessed using modified TSS, erosion score, and joint space narrowing (JSN) score[10,11]. Data from patients with radiographs at baseline and at Years 2, 4, and 5, through March 19, 2003, were included in the radiographic analysis. Radiographs were scored independently by 4 experienced radiologists or rheumatologists, who were blinded to treatment group and sequence. Radiographs from each patient were read by 2 readers, and the average score was used in the analysis. Linear extrapolations or interpolations, adjusted over time, were used to correct radiographic scores for patients whose radiographs deviated from the planned 2, 4, and 5 year timepoints. The number of patients with no radiographic progression (change in TSS $\leq$ 0) and negative progression (change in TSS $<$ 0) from baseline to Year 5 was calculated.

No imputation or estimation methods were used for missing values during the extension. All summaries of results are of patients with data available at the visit of interest (i.e., observed cases). No formal statistical comparisons were made among the 3 original treatment groups because of the observational design of the extension and the fact that the patients' decision to enter the extension was not likely to be a random event. For comparisons of the 2 year ACR responses for patients who did or did not enter the extension, a last-observation-carried-forward approach was used, as reported for the efficacy trial[6].

RESULTS

Six hundred thirty-two patients were enrolled in the efficacy study. Of these, 468 (74%) entered the extension, and 359 patients (57% of patients originally randomized to the efficacy study and 77% of those who entered the extension) remain under study as of this report (Figure 1). Of the 468 patients who entered the extension, 368 had completed the full 2 years in the efficacy study, while 100 of these patients had completed at least one year of the efficacy study, then discontinued study drug treatment (primarily for lack of efficacy), and subsequently enrolled in the extension (50 patients from the MTX group, 37 from the etanercept 10 mg group, 13 from the etanercept 25 mg group). One patient (etanercept 25 mg group) enrolled in the extension but was lost to followup.

Sixty-three percent of patients who enrolled in the extension (293 of the 468) have completed 3 years in the extension and now have 5 years of efficacy data available. The number of patients with 5 year data in each of the treatment groups is as follows: 92 of 143 patients (64%) from the MTX group, 103 of 163 (63%) from the etanercept 10 mg group, and 98 of 162 (60%) from the etanercept 25 mg group.

Patient retention (Figure 2) was the same for the groups that received either of the etanercept doses in the efficacy study, with 78% of patients in both groups continuing treatment in the extension. In contrast, only 66% of the patients from the MTX group enrolled in the extension. The majority of patients from the MTX group who did not enter the extension had not completed the required minimum of one year in the double-blind study, most discontinuing because of lack of efficacy or side effects to MTX.

The proportion of patients in the MTX group who attained ACR20 responses was lower in those who enrolled in the extension than in those who did not (52% vs 72%, respectively). The opposite was true for patients in the etanercept groups: the proportion of patients attaining an ACR20 response was higher in patients who enrolled than in those that did not (67% vs 36% in the etanercept 10 mg group and 81% vs 39% in the etanercept 25 mg group).

Baseline demographics, disease history, and RA therapy at entry to the efficacy study, for patients who enrolled in the

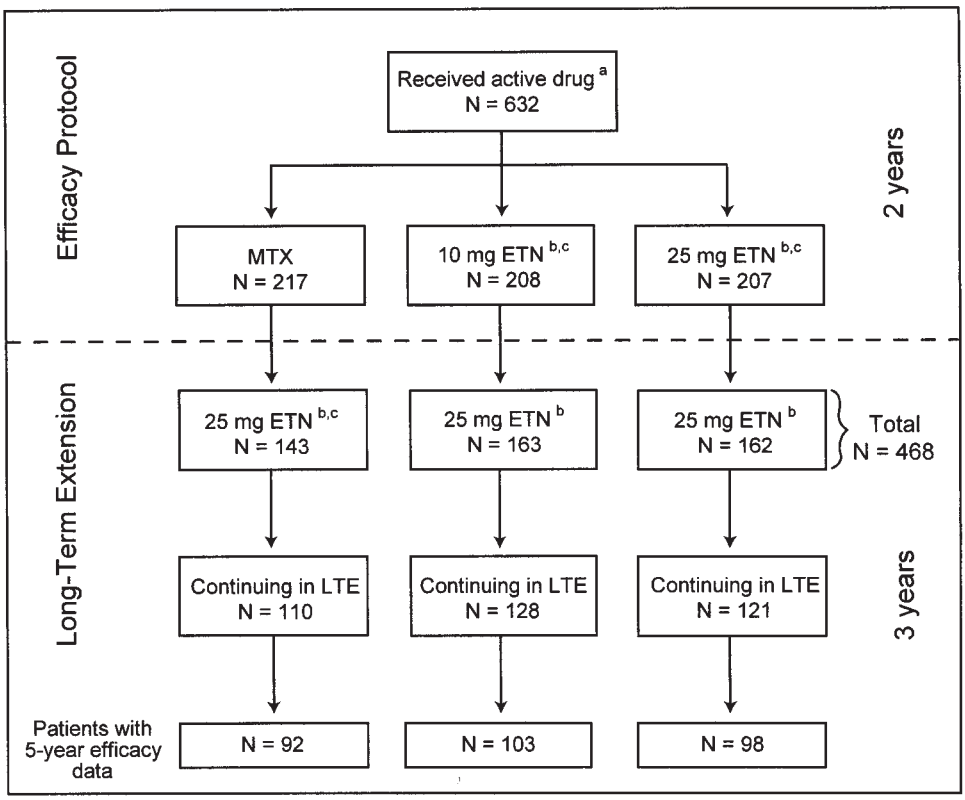

Figure 1. Patient enrollment in the efficacy study and extension. Patients were randomized to receive either MTX, 10 mg etanercept, or 25 mg etanercept in the efficacy study. After completion of 2 years in the efficacy study, patients were eligible to enroll in a longterm extension. a: Efficacy treatment protocol[2]. b: Etanercept was given twice weekly. c: 3 groups representing 558 patients who received etanercept. N: total number of patients in group, MTX: methotrexate, ETN: etanercept, LTE: longterm extension.

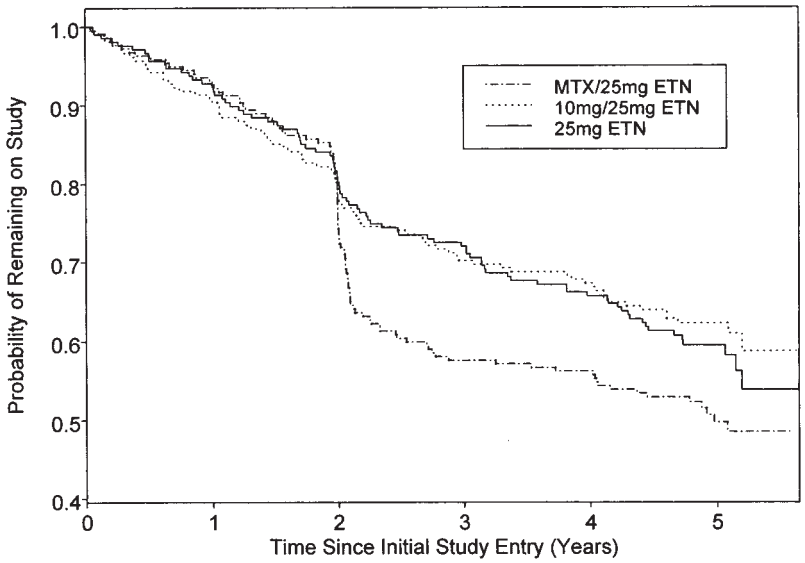

Figure 2. Kaplan-Meier estimate of the probability of a patient remaining on study. MTX/25 mg ETN refers to the group that received MTX in the efficacy study and 25 mg ETN in the extension (referred to as the MTX group in the text); 10 mg/25 mg ETN refers to the group that received 10 mg ETN in the efficacy study and 25 mg ETN in the extension (referred to as the 10 mg etanercept group in the text); 25 mg ETN refers to the group that received 25 mg ETN in both the efficacy study and the extension (referred to as the 25 mg etanercept group in the text).

extension, are shown in Table 1. Most patients were white females who tested positive for RF. Most patients in each treatment group were receiving NSAID (78% to 88%), and less than half were receiving corticosteroids (38% to 44%).

Safety. Safety results for 558 patients who received etanercept in the efficacy study or the extension (Figure 1) are shown in Table 2. Reasons for withdrawal were the following: adverse events or death (49 patients, 8.8%), patient refusal (33 patients, 5.9%), lack of efficacy (29 patients, 5.2%), physician decision (19 patients, 3.4%), lost to followup (18 patients, 3.2%), protocol issues (11 patients, 2.0%), and other (30 patients, 5.4%).

One hundred seventy-eight SAE were reported in 115 patients (20.6%) for an overall rate of 0.093 events per patient-year during the efficacy study and the extension. The most frequently reported SAE are given in Table 3. The overall SAE rate was comparable to the rate observed in the first year of the efficacy study, where 18 of 217 MTX-treated patients reported SAE (0.109 events per patient-year), and 24 of 415 etanercept-treated patients reported SAE (0.091 events per patient-year). No neurologic event associated with demyelination was reported.

Serious infections were reported for 38 patients (6.8%), a rate of 0.026 events per patient-year. The most frequent

Table 1. Demographics, disease history, and RA therapy at baseline of the efficacy study in the 468 patients who entered the extension.

	MTX Followed by 25 mg ETN, N = 143[a]	10 mg ETN Followed by 25 mg ETN, N = 163[b]	25 mg ETN Followed by 25 mg ETN, N = 162[b]
Female, n (%)	108 (76)	125 (77)	118 (73)
Caucasian, n (%)	126 (88)	139 (85)	142 (88)
Mean age, yrs (SD)	48.3 (13.1)	49.9 (12.0)	49.9 (12.1)
Range	21–80	19–84	21–82
≥ 65 yrs of age, n (%)	24 (17)	20 (12)	20 (12)
Duration of RA, median mo	7.0	7.0	7.5
No. of erosions, median (range)[c]	3.0 (0.0–46.5)	2.5 (0.0–65.0)	2.5 (0.0–55.5)
Patients with 3 or more erosions, n (%)	74 (52)	78 (48)	79 (49)
Rheumatoid factor positive, %	90	90	88
Prior No. of DMARD, mean (SD)	0.6 (0.7)	0.4 (0.6)	0.5 (0.7)
Median (range)	0.0 (0.0–3.0)	0.0 (0.0–3.0)	0.0 (0.0–3.0)
No. of patients receiving corticosteroids	63 (44)	64 (39)	61 (38)
No. of patients receiving NSAID (%)	115 (80)	127 (78)	142 (88)

[a] Patients who started etanercept treatment in the extension. [b] Patients from the 10 and 25 mg etanercept groups who enrolled into the extension. [c] Radiographs were read by 2 radiologists, and the average scores was used in the analysis. MTX: methotrexate, ETN: etanercept, N: total number of patients in group, DMARD: disease-modifying antirheumatic drug. NSAID: nonsteroidal antiinflammatory drug.

Table 2. Safety summary of all patients enrolled who received at least one dose of etanercept.

	MTX Followed by 25 mg ETN, N = 143	10 mg ETN Followed by 25 mg ETN, N = 208	25 mg ETN Followed by 25 mg ETN, N = 207	Total ETN, N = 558
Patient-years	379	768	773	1921
Withdrawals due to death or other adverse event, n (%)	6 (4.2)	17 (8.2)	26 (12.6)	49 (8.8)
Patients with SAE[a], n (%)	23 (16.1)	44 (21.2)	48 (23.2)	115 (20.6)
SAE/patient-year	0.084	0.094	0.096	0.093
Patients with serious infections[b], n (%)	7 (4.9)	13 (6.3)	18 (8.7)	38 (6.8)
Serious infections/patient-year	0.029	0.022	0.028	0.026
Patients with malignancies[c], n (%)	1 (0.7)	5 (2.4)	10 (4.8)	16 (2.9)
Malignancies/patient-year	0.003	0.008	0.014	0.009
Deaths[d], n (%)	1 (0.7)	2 (1.0)	3 (1.4)	6 (1.1)
Deaths/patient-year	0.003	0.003	0.004	0.003

[a] SAE occuring on study or within 30 days of the last dose of etanercept. [b] Infections requiring hospitalization or intravenous antibiotics occurring on study or within 30 days of the last dose of etanercept. [c] Malignancies, excluding non-melanoma skin cancers, occurring on study or within 30 days of the last dose of etanercept. [d] All deaths including 3 that occurred > 30 days after the last dose of etanercept. SAE: serious adverse events.

Table 3. Serious adverse events (SAE) experienced during the efficacy study and the extension occurring at an incidence of ≥ 0.5% of patients. Three cases of breast cancer and 3 cases of prostate cancer occurred. These events are noted in Table 4. Other SAE occurred at a frequency of 2 events or less.

Event	No. of Patients Experiencing Event	%
Any SAE	115	20.6
Pneumonia	11	2.0
Myocardial infarct	10	1.8
Bone fracture	8	1.4
Angina pectoris	6	1.1
Bronchitis	6	1.1
Cerebrovascular accident	5	0.9
Chest pain	5	0.9
Abdominal pain	4	0.7
Thrombophlebitis	4	0.7
Depression	4	0.7
Syncope	4	0.7
Cholecystitis	3	0.5
Colitis	3	0.5
Pyelonephritis	3	0.5

types of infections were the following: lower respiratory tract infection excluding pneumonia (0.004 events per patient-year), pneumonia (0.007 events per patient-year), urinary tract infection (0.004 events per patient-year), and skin and soft tissue infections (0.004 events per patient-year). There were no reports of tuberculosis, histoplasmosis, listeriosis, or other opportunistic infections.

The overall exposure-adjusted rate of serious infections in adult patients (0.026 events per patient-year) was comparable to the rates observed for the MTX group (0.031 events/patient-year) and the combined etanercept groups (0.024 events per patient-year) in the first year of the efficacy study.

Eighteen malignancies (excluding 10 non-melanoma skin cancers and including one *in situ* carcinoma) were reported in 16 patients (3%) during the study or within 30 days of the last dose of etanercept (0.009 events per patient-year). The types of malignancies reported are shown in Table 4. The number of malignancies observed was compared with expectations for cancers in an age and sex matched cohort from the general population, using the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database[12]. The expected number calculated from the SEER database, which excludes *in situ* carcinomas, was 14.

Two cases of malignant melanoma were reported, one of which was *in situ*. Rates of non-melanoma skin cancers were assessed through the first year of the extension (1594 patient-years). No case of squamous cell carcinoma and 10 cases of basal cell skin carcinoma were reported. The expected number of basal cell skin carcinomas was 20.3, calculated for an age and sex matched cohort from the general population using data from the Southeastern Arizona Skin Cancer Registry[13].

Table 4. Cancers reported during the efficacy study and the extension. Eighteen malignancies occurred in 16 patients. One patient had both prostate and colon cancer, and another patient had both prostate cancer and malignant melanoma.

Event	No. of Events
Breast cancer	3
Prostate cancer	3
Colon cancer	3
Lung cancer	2
Malignant melanoma (1 in situ)	2
Chronic lymphocytic leukemia (T cell)	1
Kidney cancer	1
Hodgkin's lymphoma	1
Lymphoma (B cell)	1
Invasive adenocarcinoma (not otherwise specified)	1
Total	18

Two lymphomas (one Hodgkin's and one non-Hodgkin's) were reported. One additional lymphoma occurred more than 30 days after the last dose of etanercept. The number of lymphomas observed is higher than would be expected for the number calculated for the general population (the expected number calculated from the SEER database was 0.6). The standardized incidence ratio (SIR, the ratio between observed and expected events) for the number of lymphomas observed in this study relative to the number expected in the general population was 3.3. However, RA patients are known to have a higher incidence of lymphoma than the general population[14].

Six deaths were reported among all 558 patients (1.1%) in the extension (0.003 deaths per patient-year), including 3 patients who died more than 30 days after their last dose of etanercept. The causes of death were as follows: complications following repair of aortic aneurysm, lung carcinoma, retroperitoneal bleed, congestive heart failure, respiratory failure, and ruptured cerebral aneurysm. The expected number of deaths for the general population, adjusted for age and sex, calculated based on data from National Vital Statistics Reports[15], was 17.

ACR scores and disease activity measures. ACR scores remained relatively constant from the beginning of the extension (Year 2) through Year 5 (Figure 3). At Year 5, ACR20, 50, and 70 scores were 65%, 52%, and 37%, respectively, for the group that received MTX through Year 2 and then added etanercept (MTX group); 74%, 57%, and 32% for the etanercept 10 mg group; and 68%, 49%, and 33% for the etanercept 25 mg group.

In each of the treatment groups, the median values for number of swollen joints, CRP, HAQ score, and DAS28 CRP all showed rapid improvements by Year 1 that were sustained through Year 5 (Figure 4).

Methotrexate use. Patients in the MTX group of the efficacy

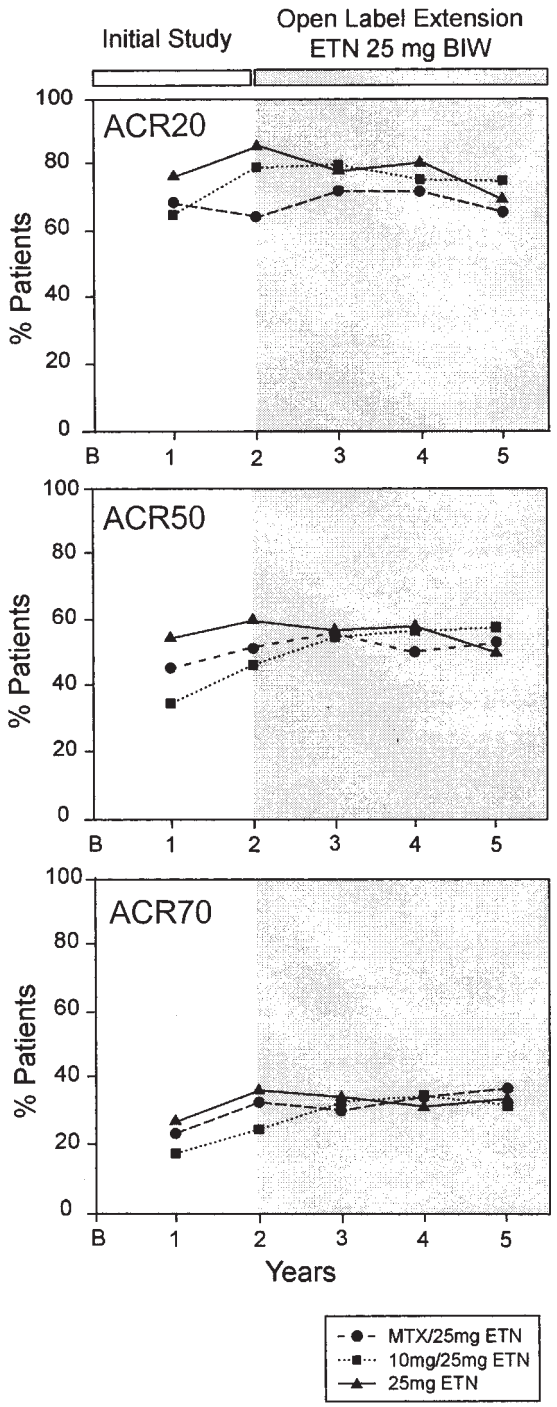

Figure 3. ACR scores of patients during the efficacy study and the extension. ACR scores were sustained for up to 5 years. ACR20, 50, and 70 scores are the proportion of patients achieving 20%, 50%, or 70% improvement in the ACR composite score compared with baseline of the efficacy study. Patients received 25 mg etanercept twice weekly during the extension (shaded time period) and were permitted to receive other RA medications during the extension (see Results). N = 92 for the MTX/25 mg ETN group, N = 103 for the 10 mg/25 mg ETN group, and N = 98 for the 25 mg ETN group. ETN: etanercept, BIW: twice weekly, MTX: methotrexate.

study continued to receive MTX at the beginning of the extension; however, most of these patients decreased or discontinued MTX during the first year of treatment with etanercept. After one year in the extension, 57% of patients (75 of 132) had discontinued MTX and 15% (20 of 132) decreased but did not discontinue MTX. After 3 years in the extension, 83% of patients (91 of 110) had decreased their dose or discontinued MTX, whereas 5% of patients (5 of 110) had increased their dose of MTX. The mean dose of MTX decreased from 17.6 mg/week (median 20.0 mg/week) at the beginning of the extension to 4.9 mg/week (median 0.0 mg/week) after 3 years in the extension.

ACR scores remained stable during tapering of MTX. For example, the ACR20 score after 3 years of treatment in the extension was 69% for the group who decreased or discontinued MTX (n = 91) and 65% for the entire group (n = 143).

Most patients in the 10 and 25 mg etanercept groups did not receive MTX during the extension. However, at the time of this analysis, 17% (27 of 163) of patients in the etanercept 10 mg group and 20% (32 of 162) in the etanercept 25 mg group received MTX at some point during the extension.

Corticosteroid use. Less than half of the patients were receiving corticosteroids at the beginning of the extension: 64 of 143 (45%) in the MTX group, 71 of 163 (44%) in the etanercept 10 mg group, and 61 of 162 (38%) in the etanercept 25 mg group). The mean prednisone equivalent doses for these groups ranged from 5.3 to 6.4 mg/day at the beginning of the extension.

Corticosteroid use was examined in patients in the etanercept 25 mg group who were receiving corticosteroids when they began the efficacy study (n = 80). After one year of etanercept treatment in the efficacy study, 50% of patients had decreased their dose or discontinued corticosteroids. After 5 years of etanercept treatment, 75% of patients had decreased or discontinued corticosteroids. The mean dose of corticosteroids for these patients decreased from 8.6 mg/day (median 7.5 mg/day) at baseline of the efficacy study, to 2.4 mg/day (median 0.0 mg/day) after 5 years of etanercept treatment.

ACR scores remained stable despite tapering of corticosteroids. For patients who received etanercept for 5 years, the ACR20 scores were 70% for those who discontinued or tapered corticosteroids and 68% in the group as a whole.

Radiographic findings. The mean baseline TSS for all patients enrolled in the efficacy study ranged from 11.2 to 12.9 Sharp units, the mean erosion score ranged from 6.1 to 7.5 units, and the mean JSN score ranged from 5.0 to 6.0 units. Radiographic data through 5 years were available for 297 patients (91 in the MTX group, 106 in the etanercept 10 mg group, and 100 in the etanercept 25 mg group). Baseline radiographic data from the subset of patients who remained under study for 5 years were similar to the data from all patients enrolled. For the subset who remained on treatment

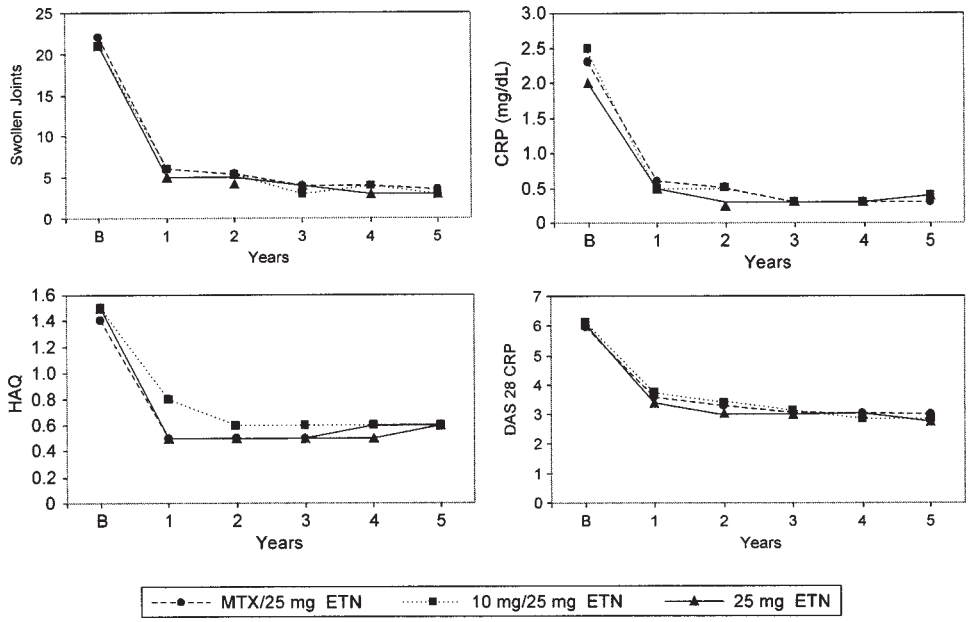

Figure 4. Median number of swollen joints, CRP, HAQ, and DAS28 CRP over time. The ACR components show sustained improvement up to 5 years. Patients were permitted to receive other RA medications during the extension (see Results). N = 92 for the MTX/25 mg ETN group, N = 103 for the 10 mg/25 mg ETN group, and N = 98 for the 25 mg ETN group. B: baseline, CRP: C-reactive protein, HAQ: Health Assessment Questionnaire, DAS28 CRP: Disease Activity Score based on assessment of 28 joints and CRP, ETN: etanercept.

through Year 5, the mean (SD) TSS at baseline was 13.0 (18.4) in the MTX group, 10.0 (16.8) in the etanercept 10 mg group, and 14.6 (22.9) in the etanercept 25 mg group. Similarly, the mean (SD) erosion scores at baseline were 7.3 (10.6), 5.9 (9.4), and 7.4 (13.0), and JSN scores were 5.7 (9.7), 4.1 (9.1), and 7.2 (10.9) for the MTX and the etanercept 10 mg and 25 mg groups, respectively.

Radiographic progression, expressed as mean change from baseline in TSS, erosion score, and joint space narrowing score, is illustrated in Figure 5. The mean rate of progression of TSS (the slope) decreased in the etanercept 10 mg and MTX groups after Year 2, when treatment with etanercept 25 mg was started. The mean rates of progression of TSS from Years 2 to 5 were generally similar in the 3 groups. The etanercept 25 mg group had a mean rate of progression of TSS of 0.63 Sharp unit/year from baseline to Year 2 and 0.58 Sharp unit/year from Years 2 to 5.

The mean annual rate of progression was < 1.0 TSS unit/year for patients who received MTX or etanercept 25 mg, alone or in combination, indicating significant inhibition of radiographic progression. Annual progression for patients from the etanercept 10 mg group was > 1.0 TSS unit/year. These findings suggest that an etanercept dose of 25 mg twice weekly is more effective than 10 mg twice weekly with respect to slowing radiographic progression. The proportion of patients with no progression in TSS (change in TSS ≤ 0) from baseline to Year 5 was similar between groups and was 55% overall (162 of 297 patients).

Eleven percent of patients (32 of 297) had a negative change in TSS from baseline to Year 5 (12 in the MTX group, 13 in the etanercept 10 mg group, and 7 in the etanercept 25 mg group). During the extension, MTX use in these patients showed a different pattern between treatment groups. All 12 patients in the MTX group received MTX at some point in the extension. However, only 2 of 13 patients (15%) in the etanercept 10 mg group and 2 of 7 patients (29%) in the etanercept 25 mg group received MTX at some point during the extension.

Radiographic images of 2 proximal interphalangeal (PIP) joints from a 50-year-old male patient from the etanercept 10 mg group are shown in Figure 6. At baseline, this patient had a disease duration of 2 months, positive serum RF, and no previous DMARD exposure. Active disease was evident at baseline: the patient had 39 tender joints, 29 swollen joints, serum CRP 4.5 mg/dl, and ESR of 77 mm/h. The baseline HAQ score was 0.88 and the DAS28 CRP was 6.7.

After one month of etanercept treatment, the patient showed dramatic clinical improvement and achieved an ACR70 response with no tender or swollen joints. The clinical improvements were maintained for 4 years of treatment, when his HAQ score was 0 and DAS28 CRP score was 1.2.

Radiographic scores for this patient were improved after 4 years of etanercept treatment. The baseline TSS was 30 (erosion score 15, JSN score 15) compared with a 4 year TSS of 21 (erosion score 10, JSN score 11). Examination of the radiographs from these timepoints revealed examples of

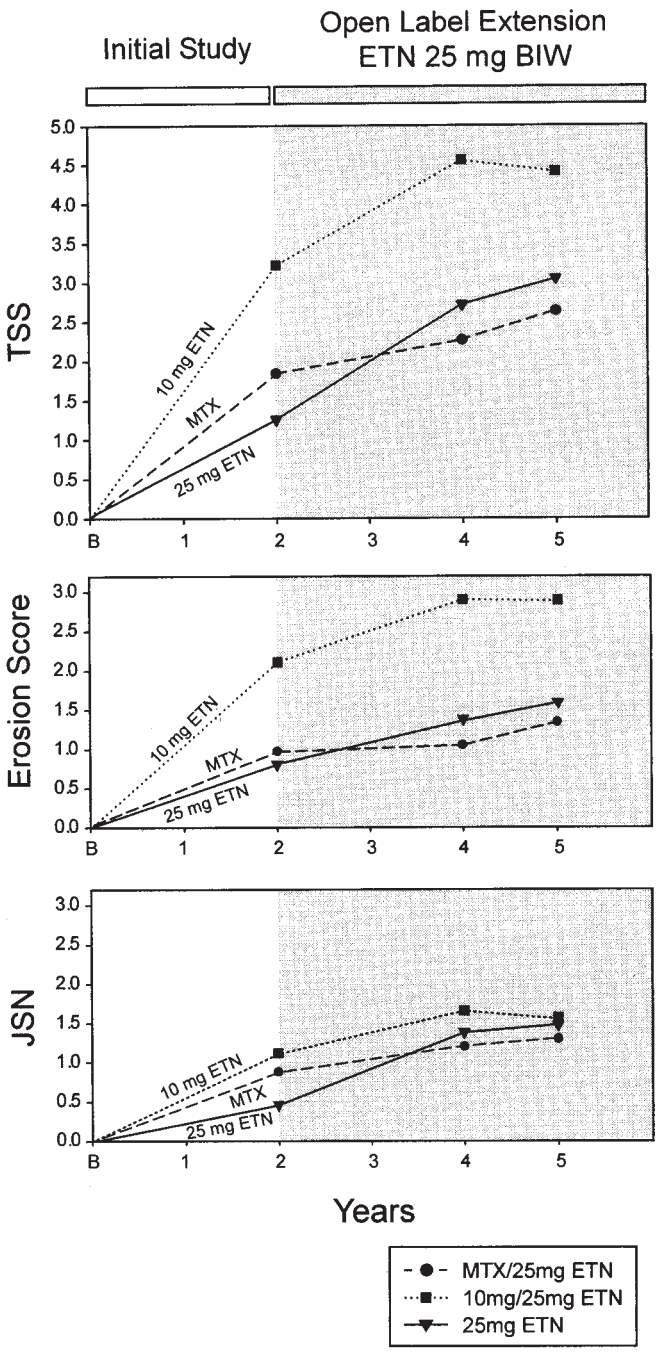

Figure 5. Mean changes from baseline for Total Sharp Score (TSS), erosion score, and joint space narrowing (JSN). Shaded portion of the graph represents the extension, where all patients were receiving 25 mg ETN twice weekly (BIW). Baseline values are given in Results. Patients were permitted to receive other RA medications during the extension (see Results). N = 91 for the MTX group, N = 106 in the 10 mg ETN group, and N = 100 in the 25 mg ETN group, at Year 5.

PIP with damage at baseline that was markedly improved at Year 4 (Figure 6).

DISCUSSION

This cohort of patients was DMARD-naive and had early aggressive RA characterized by significant clinical symptoms (at least 10 swollen and 12 tender joints with 3 or more erosions or positive RF) at entry to the efficacy study. As reported[6], patients treated with etanercept achieved rapid and sustained improvements in disease activity for up to 2 years, and treatment with etanercept was generally well tolerated. This cohort was followed for an additional 3 years of treatment, during which etanercept continued to be generally well tolerated. This analysis showed that in patients who continued taking etanercept, the rates of SAE, serious infections, cancer, deaths, and withdrawals due to adverse events remained stable over time, and were similar to rates reported for the blinded portion of the efficacy study.

The overall observed rate of serious infections (0.026 events per patient-year) was also similar to the rate reported for 2 cohorts of RA patients. The Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) database[16], a prospectively defined cohort of 5569 RA patients with data on infections requiring hospitalization, reported a rate of 0.031 events per patient-year (26,419 patient-years). The Olmsted County cohort is a retrospectively defined, population based group of 609 RA patients, where the rate of serious infections was 0.096 (7730 patient-years)[17]. While the rate of serious infections observed in our study appeared to be lower than the rate reported for the Olmsted County cohort, the patients in our study were younger and likely to have less comorbidity on average, and therefore may have been less likely to develop infections. There were no reports of tuberculosis, histoplasmosis, listeriosis, or other opportunistic infections in this study.

The observed numbers of malignancies were within the range expected for the general population[13], with the exception of lymphomas. For lymphomas, the SIR for this patient group relative to the rate expected in the general population was 3.3. Similarly, the SIR calculated from the overall clinical trial experience with etanercept through December 2002 was 2.3 (95% CI 0.55 to 5.03; 8295 patient-years) relative to the rate expected in the general population[18]. Although it is recognized that RA patients have a higher incidence of lymphoma than the general population, the relationship between disease severity, RA medications, and lymphoma remains in question. Lymphoma rates for patients with RA were examined in an analysis of 18,572 patients who participated in the National Data Bank for Rheumatic Diseases from the practices of 908 US rheumatologists[14]. In this analysis, the overall SIR for patients with RA was 1.9 (95% CI 1.3 to 2.7), and the SIR for patients receiving biologics was 2.9 (95% CI 1.7 to 4.9) relative to the rate expected in the general population. Examination of risks for lymphoma in patients from the National Data Bank for Rheumatic Diseases who were receiving MTX or anti-TNF therapy failed to establish a causal relationship between RA treatments and the development of lymphoma[14].

Improvement in disease activity remained constant dur-

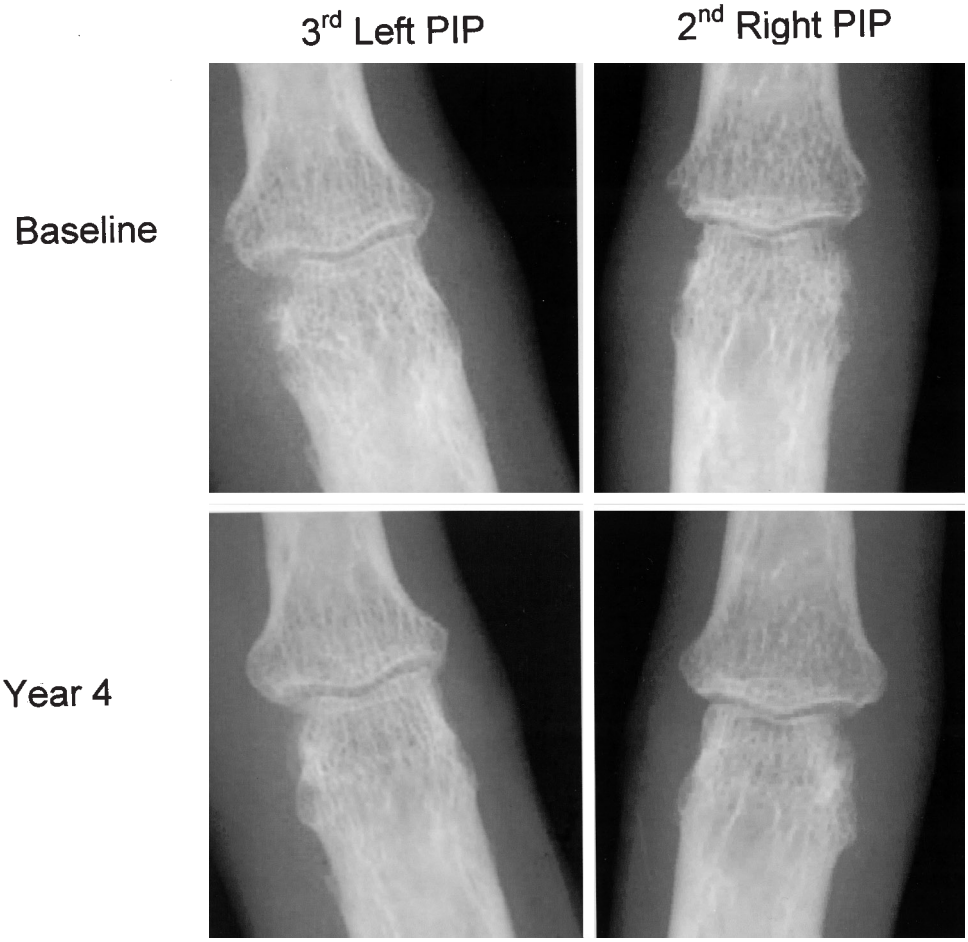

Figure 6. Left panels show radiographs of the 3rd left proximal interphalangeal (PIP) joint. At baseline the radial and ulnar surfaces show irregularity and scalloping with disruption of the cortex. At 4 years the irregularities are markedly improved and recortication is evident. Right panels show radiographs of the 2nd right PIP joint. At baseline the radial surface of the joint shows irregularity and cortical disruption. At 4 years recortication is evident.

ing longterm treatment with etanercept: ACR responses, DAS28 CRP scores, and individual components of the ACR composite score all showed early improvements that were sustained for the duration of etanercept treatment.

Estimated yearly rates of radiographic progression for these patients (calculated from duration of RA and baseline TSS) were 8 to 9 units/year at baseline of the efficacy study[6]. However, it should be acknowledged that it is difficult to estimate rates of progression, particularly in early disease when the exact date of disease onset cannot be definitively established. The observed rate of progression of TSS in this analysis was < 1 unit/year from baseline to Year 5 in the groups treated with MTX and etanercept 25 mg (alone or in combination). This rate of radiographic progression appears to be lower than other published rates for patients with early RA. In a study of early RA patients who were randomized to receive hydroxychloroquine, aurothioglucose, or MTX (up to 15 mg/week), the mean rate of progression in TSS was 8.6 units/year over a 6 year period[19]. In another study of patients with definite or probable early-stage RA who were receiving chloroquine or sulfasalazine, the mean rate of progression in TSS was about 4.8 Sharp units after one year[20].

The mean progression of TSS in the etanercept 10 mg group was higher than the MTX or etanercept 25 mg groups during the first 2 years of treatment, indicating that significantly more progression had occurred[6]. Additionally, in this analysis, the rate of progression for the 10 mg group decreased after initiation of 25 mg etanercept at Year 2. The group treated with 25 mg etanercept showed the least progression from baseline to Year 2, and the rate of progression remained low from Years 2 to 5.

The MTX group had the largest decrease in progression of TSS after initiation of etanercept (Figure 5). This may be due in part to some patients receiving combination treatment with MTX and etanercept at the beginning of the extension. Treating RA patients with both MTX and etanercept has been shown to have an outstanding effect on reducing the

rate of radiographic progression[3]. The low rate of progression in patients in the MTX group is notable because these patients were clinically worse than patients in the MTX group who did not enter the extension, and had a trend towards worse radiographic outcomes at 2 years. In Figure 5, the apparent inflexion point in the slope at 2 years for the etanercept 10 mg and MTX groups implies that some degree of potential benefit was lost compared to how these patients would be expected to have progressed had they been treated with 25 mg etanercept for the full 5 years. The observation that early aggressive therapy may have long-lasting effects has also been reported from the COBRA trial[21].

In our analysis, some patients in each treatment group had negative changes from baseline in TSS after 5 years of treatment, raising the possibility that structural repair might be occurring, in addition to halting of radiographic progression. The baseline radiograph of a patient who started etanercept that showed erosions that were markedly improved 4 years later (Figure 6) allows speculation that repair may have occurred in response to treatment with etanercept. Radiographs from patients in this trial were reexamined as part of a workshop on repair of erosions held by the Outcomes Measures in Rheumatology (OMERACT) imaging committee in New Town, Pennsylvania, in 2004. During this workshop, 5 of 6 experts identified the radiographs from this patient as indicative of repair (Tsuji W, personal communication).

A more detailed analysis relating the sizes of the observed changes in TSS and the minimally detectable differences of the radiograph reading technique would be required to show conclusively whether clinically important repair does indeed occur. While one would not expect to regain normal joint function as a consequence of repair, inhibition of progression early in the course of the disease could lead to improved patient function years later.

During treatment with etanercept, patients who were initially receiving concomitant MTX or corticosteroids were able to reduce their doses, and a substantial number of patients discontinued these concomitant therapies while maintaining their clinical responses. Although recent data clearly show that a combination of etanercept and MTX is superior to etanercept alone for the treatment of RA[3], decreasing or discontinuing MTX provides a treatment option for patients who are unable to tolerate MTX. Since use of corticosteroids for the treatment of RA is associated with adverse events, the ability to decrease or discontinue corticosteroids, where appropriate, confers a potential benefit to patients and is an achievable goal of RA treatment in many patients.

The efficacy analyses presented here are based on patients who remained under treatment at Year 5 and had sufficient data to be included in the analysis. Interpretation of these results suffers from the limitations of a completer analysis. Efficacy responses observed in patients remaining in the extension are likely to overestimate efficacy responses expected in the general early RA population, since patients with poor responses are more likely to withdraw. As well, it is important to recognize that efficacy responses reported at Year 5 are based on roughly half the patients who had originally enrolled in the efficacy trial.

Longterm safety and efficacy outcomes in patients with chronic diseases such as RA provide important information for treatment decisions. In this study, 77% of patients (359/468) entering the extension remained on study after 3 years. This high persistence rate leaves open the possibility for collection of data over longer periods of time and gives hope to even longer durability of a significant clinical response.

For early RA patients treated for up to 5 years with etanercept, safety findings were consistent with those reported for patients with RA in general; no increases in rates of SAE or infections occurred over time. Etanercept treatment in patients with early RA resulted in sustained efficacy responses, with an ACR50 of 49% in the group of patients who received etanercept for 5 years. Radiographic analysis showed a substantial reduction in the rate of progression of joint damage compared with rates for early RA patients not treated aggressively or effectively. It is noteworthy that a small group of patients actually showed negative rates of radiographic progression, suggesting that cessation of new erosions and repair of old erosions may be possible, and emphasizing the influence of early treatment with biological therapy in patients with early RA.

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