

Safety and Efficacy of Etanercept Treatment in Elderly Subjects with Rheumatoid Arthritis

JOAN M. BATHON, ROY M. FLEISCHMANN, DÉsirÉE M. van der HEIJDE, JOHN R. TESSER, PAUL M. PELOSO, YUN CHON, and BARBARA WHITE

ABSTRACT. Objective. To evaluate safety and efficacy of etanercept treatment in elderly (age \geq 65 yrs) and younger adult subjects (age $<$ 65 yrs) with rheumatoid arthritis (RA).

Methods. Subset analyses were used to describe the safety and efficacy of etanercept in elderly and younger subjects treated for early and disease modifying antirheumatic drug-resistant or late-stage RA (ERA and LRA) in one of 4 randomized controlled clinical studies (N = 1353) or 2 longterm extensions (N = 1049).

Results. Rates of serious adverse events tended to be higher in elderly than younger subjects; however, rates of safety events observed in elderly etanercept-treated subjects did not exceed rates in elderly placebo or methotrexate (MTX)-treated subjects. With regard to efficacy measures [American College of Rheumatology 20% response (ACR20), ACR50, and ACR70], elderly subjects tended to have somewhat less robust responses to treatment than younger subjects. However, for both age groups, treatment with etanercept resulted in improved efficacy and function compared with control treatment, and combination therapy with etanercept plus MTX resulted in greater efficacy than either etanercept or MTX used alone. Efficacy responses of elderly subjects were sustained for up to 6 years. Radiographic progression (measured using modified Sharp Score) after one year of treatment was lower in subjects treated with both etanercept and MTX compared with subjects treated with either agent used alone, and this pattern was similar in both age groups.

Conclusion. Consistent with responses in younger subjects, elderly subjects with RA treated with etanercept experienced significant improvement in disease activity and function without incurring additional safety concerns. (J Rheumatol 2006;33:234–43)

Key Indexing Terms:

ETANERCEPT

RHEUMATOID ARTHRITIS

ELDERLY

Rheumatoid arthritis (RA) is an erosive disease that predominantly involves the synovial tissue of joints and is characterized by variable disease onset and clinical course, potentially resulting in structural joint destruction and subsequent permanent disability¹. The cause of the disease remains unknown; however, the pathogenic involvement of cytokines in RA, especially tumor necrosis factor (TNF) has gained wide acceptance². A key role of TNF in RA is further

supported by the efficacy of anti-TNF therapies in improving signs and symptoms of RA, improving patient function, and halting progressive joint damage³⁻⁹.

Epidemiologic studies have shown that RA is most prevalent in those who are 65 years of age or older^{10,11}. The disease is commonly diagnosed between the ages of 30 and 50, but up to 33% of subjects may be diagnosed after the age of 60 years^{12,13}. Elderly patients, however, may have a greater likelihood of comorbid illnesses than younger patients, and may therefore have a higher risk of adverse events including infection. Given the effectiveness of anti-TNF therapies in treating RA, examination of the benefits and risks in elderly patients is important because the elderly may be disproportionately vulnerable to adverse events when they receive anti-TNF therapies.

The safety and efficacy of anti-TNF therapies in elderly patients with RA has not been well described, with the exception of one study by Fleischmann, *et al*¹⁴ describing results of etanercept (Enbrel[®], a soluble p75 TNF receptor fusion protein that binds and neutralizes TNF and lymphotoxin-a) treatment in 197 patients age 65 years or older. That report did not include data from the recent Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) that included combination treatment

From the Division of Rheumatology, Johns Hopkins University, Baltimore, Maryland; Division of Rheumatology, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, USA; Rheumatology Department, University Hospital, Maastricht, The Netherlands; Phoenix Center for Clinical Research, Phoenix, Arizona; and Amgen Inc., Thousand Oaks, California, USA.

Supported by Immunex Corporation, a wholly owned subsidiary of Amgen Inc., and by Wyeth, Collegeville, PA, USA.

J.M. Bathon, MD, Division of Rheumatology, Johns Hopkins University; R.M. Fleischmann, MD, Division of Rheumatology, University of Texas Southwestern Medical Center at Dallas; D.M. van der Heijde, MD, Rheumatology Department, University Hospital, Maastricht; J.R. Tesser, MD, Phoenix Center for Clinical Research; P.M. Peloso, MD; Y. Chon, PhD; B. White, MD, Amgen Inc.

Address reprints requests to Dr. J. Bathon, Division of Rheumatology, Johns Hopkins University, Ste. 1B13, 5501 Hopkins Bayview Circle, Baltimore, MD 21224. E-mail: jrbathon@jhmi.edu

Accepted for publication August 23, 2005.

with anti-TNF plus methotrexate (MTX) therapy, and did not compare efficacy and rates of infection across treatment assignments within the same studies.

To address the issue of risks and benefits of TNF inhibition with etanercept in elderly RA patients, data from RA subjects who participated in 4 randomized, controlled clinical studies of etanercept^{3,4,6,8} and 2 longterm observational extensions were examined. Data from elderly (age \geq 65 yrs) and younger adult subjects were analyzed separately. The objectives of this subset analysis were as follows: (1) to assess whether etanercept treatment is associated with a different rate of serious adverse events (SAE) or serious infectious episodes (SIE) in elderly versus younger RA subjects; (2) to assess whether etanercept treatment improves signs and symptoms of inflammation and functional disability, and reduces progressive joint damage, to similar degrees in elderly and younger RA subjects; (3) to evaluate whether etanercept treatment is effective in both elderly and younger subjects who have recent onset RA or disease modifying antirheumatic drug (DMARD)-refractory RA; and (4) to compare efficacy responses to combination treatment with etanercept plus MTX versus responses to etanercept or MTX monotherapy in both elderly and younger subjects.

MATERIALS AND METHODS

Subjects and studies. All subjects gave written informed consent at the time of enrollment into these studies, before any study related procedures were performed. Institutional review boards or institutional ethics committees approved the protocols. Adult subjects enrolled in these studies had RA and were evaluated according to age at the time of entry into the first controlled study in which they were enrolled. For this analysis, elderly subjects were defined as those \geq 65 years of age and younger subjects were defined as those \geq 18 and $<$ 65 years of age.

Results are presented for elderly and younger RA subjects who participated in one of 4 randomized, controlled clinical trials or 2 open-label extensions with etanercept. Studies 016.009⁴ and 16.0014³, together called LRA for late RA, were conducted in DMARD-failure RA subjects and MTX-incomplete responders, respectively. These studies were chosen because the dosing arms included the marketed dose for RA (25 mg etanercept twice weekly) and placebo. Participation in these studies, or 4 uncontrolled or early phase studies with DMARD-failure RA subjects (studies 016.0002, 016.0004, 016.0008, and 016.0019), allowed subjects to enter the LRA extension. The early RA study (ERA, study number 016.0012⁶) compared MTX and etanercept therapy. It was the sole study through which subjects entered the ERA extension. The TEMPO study included subjects who had failed at least one DMARD other than MTX⁸.

Although the previously published reports from these studies did not investigate age as a predictor of efficacy or adverse events, this analysis focuses on qualitative comparison of elderly and younger subjects. Subjects in this report received control treatment (placebo or MTX) or etanercept at 25 mg twice weekly during one of the 4 randomized controlled studies. Subjects received etanercept 25 mg twice weekly during one of the open-label extension studies. Data from visits through May 28, 2004, are included in this analysis.

Safety. Safety events with a start date on or after each subject received the first dose of study drug were included in the safety analysis. SAE were classified using a modified version of the Coding Symbols for a Thesaurus of Adverse Reactions Terms (COSTART)¹⁵ and are presented as rates.

SIE were defined as those SAE requiring intravenous antibiotics or hospitalization. To be conservative, infections requiring intravenous anti-

otics or hospitalization that did not meet the definition of SAE are also included for the controlled studies and part of the extension studies (note only SAE were recorded for the latter portions of the extensions). Opportunistic infections were identified by manual review of SAE. Herpes zoster of the skin was not considered an opportunistic infection.

The number of cases of cancer observed (excluding nonmelanomatous skin cancers) was compared with expectations for cancers in age and sex matched cohorts from the general population, using the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database¹⁶.

The incidence of cardiovascular events included any potentially cardiac related COSTART terms.

Efficacy. Efficacy assessments for the controlled studies and the ERA extension were measured relative to the baseline of the initial study. Efficacy assessments for the LRA extension were measured relative to the baseline values of the study in which etanercept was initiated, except for 90 subjects who had a gap of more than one year between the initial and extension studies. For these subjects, efficacy measures were relative to baseline values when continuous etanercept dosing was initiated.

Efficacy was assessed using the ACR response criteria¹⁷. ACR responses 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. Health Assessment Questionnaire (HAQ) scores were calculated.

Radiographic outcomes were assessed in the ERA and TEMPO studies. However, the number of elderly subjects with radiographic data in the ERA study was too small (31 MTX subjects, 34 etanercept subjects) for meaningful analyses to be performed, so only the TEMPO radiographic results are presented. The primary radiographic endpoint in the TEMPO study was progression from baseline in total joint damage score (modified total Sharp Score = joint erosion score + joint narrowing score¹⁸) at one year⁸. Radiographs of the hands, wrists, and feet were obtained at baseline, at 6 months, and at one year, or at the final study visit. Digitized random radiographs were read as described⁸.

Statistical methods. Data from controlled trials and extensions were examined to qualitatively describe safety and efficacy outcomes. Given the post-hoc design of the analysis, a descriptive approach was taken rather than inferential hypothesis testing. Baseline demographics and disease history were obtained at enrollment into the initial study, except for the LRA extension, where baseline values were those obtained from the first study in which the subject received continuous etanercept. Study drug exposure was calculated for the controlled trials. Etanercept exposure for the extension was calculated as the time interval from the first dose of etanercept in any study to the most recent drug dose dates available as of time of database closure; time taking placebo or MTX in the control arms did not contribute to cumulative etanercept exposure.

Efficacy responses were calculated using last observation carried forward for the controlled portions of the clinical studies and are presented as "observed cases" with no imputation for the extensions. Results from subjects in the LRA, ERA, TEMPO, and the LRA and ERA extensions were reported separately.

RESULTS

Subject demographics and disease characteristics. Subject enrollment in the controlled clinical studies and the open-label extensions is shown in Table 1. This analysis included all subjects enrolled in the controlled LRA studies (N = 247) and TEMPO (N = 682). However, for the ERA study, subjects from the MTX and 25 mg etanercept arm were included (N = 424), whereas subjects in the 10 mg etanercept group were not included, since this is not the approved dose. The LRA extension included 581 adult subjects and the ERA extension 468 subjects. Elderly subjects made up 14% to 22% of the subjects across the treatment arms.

Table 1. Baseline demographics, disease characteristics, and concomitant RA medications in elderly and younger subjects with RA.

	LRA		LRA Extension*	ERA		ERA Extension*	TEMPO		
	Placebo	ETN	ETN	MTX	ETN	ETN	MTX	ETN	MTX + ETN
Total enrollment	110	137	581	217	207	468	228	223	231
N (% of total patients in arm)									
≥ age 65	19 (17)	20 (15)	93 (16)	32 (15)	37 (18)	64 (14)	47 (21)	50 (22)	44 (19)
< age 65	91 (83)	117 (85)	488 (84)	185 (85)	170 (82)	404 (86)	181 (79)	173 (78)	187 (81)
Age**, median (range), yrs									
≥ age 65	68 (65–77)	69 (65–78)	69 (65–86)	70 (65–80)	71 (65–82)	69 (65–84)	70 (65–82)	69 (65–81)	68 (65–80)
< 65	48 (28–64)	49 (26–64)	49 (18–64)	47 (21–64)	47 (21–64)	47 (19–64)	49 (20–64)	50 (21–64)	51 (19–64)
Duration of RA, median (range), yrs									
≥ age 65	11.0 (1–31)	9.5 (3–43)	10.5 (1–46)	0.3 (0–3)	0.8 (0.1–4)	0.5 (0–4)	6.2 (0.4–18)	5.7 (0.5–18)	5.4 (0.4–19)
< age 65	9.0 (1–57)	10.0 (1–33)	10.0 (0–58)	0.8 (0–4)	0.7 (0–4)	0.6 (0–4)	4.8 (0.4–26)	4.5 (0.3–20)	5.9 (0.5–23)
Prior no. DMARD, median (range)									
≥ age 65	3.0 (1–5)	3.0 (1–6)	3.0 (1–8)	0 (0–2)	1.0 (0–3)	0.5 (0–3)	2.0 (0–8)	2.0 (1–6)	2.0 (0–5)
< age 65	3.0 (1–7)	3.0 (1–7)	3.0 (0–8)	1.0 (0–3)	0 (0–3)	0 (0–3)	2.0 (0–9)	2.0 (0–7)	2.0 (0–7)
Methotrexate (% subjects receiving)									
≥ age 65	32	20	N/A	0	0	0	43	52	36
< age 65	26	47	N/A	0	0	0	42	39	45
Corticosteroids (% subjects receiving)									
≥ age 65	79	75	52 [†]	63	57	50 [†]	75	68	59
< age 65	57	68	53 [†]	38	35	39 [†]	57	47	60

* Baseline demographics and disease history were obtained at enrollment into the initial study, except for the LRA extension, where baseline values were obtained from the first study in which the subject received etanercept. The ERA extension included subjects from all treatment arms in the initial study. The LRA extension included subjects from the controlled trials described in this report as well as others from other etanercept trials in DMARD-refractory subjects (see Materials and Methods). ** Age is given as of time of entry into initial controlled clinical study, in which subject may have received therapy other than etanercept. † Corticosteroid use was counted as positive for a subject if corticosteroids were used at any visit in the protocol for which the subject had the longest etanercept exposure. LRA: DMARD-resistant RA, ERA: early RA, TEMPO: Study of Etanercept and Methotrexate with Radiographic Patient Outcomes, ETN: etanercept, MTX: methotrexate.

Baseline characteristics, other than age, were similar between the age groups within each study (Table 1). Across treatment groups and studies, 84% to 100% of subjects were Caucasian, 61% to 83% were women, and 71% to 95% were seropositive for rheumatoid factor. The duration of RA and DMARD history were similar in elderly and younger subjects within each study. Other demographic and disease characteristics at the time of entry into the different studies are given in Table 1.

Safety assessments. The controlled, randomized, double-blind studies and open-label extensions included in this analysis represent 5815 patient-years of etanercept exposure. The duration of study drug exposure and event rates for SAE, SIE, and cancer for each treatment arm are given in Tables 2A and 2B. In the controlled arms of the LRA and ERA studies, the rates of SAE tended to be higher in elderly than in younger subjects. Comparisons between treatment arms in the LRA controlled trial showed that the rate of SAE appeared to be slightly higher in the placebo-treated group compared with the etanercept-treated group for elderly subjects, whereas the rates were comparable in both treatment groups in the younger subjects. In the controlled ERA trial, the rate of SAE was slightly higher in the MTX-treated subjects for both age groups. In the TEMPO study, the rates of SAE were similar in elderly and younger subjects treated with MTX. In contrast, SAE rates appeared higher in the

elderly versus younger subjects in the etanercept and etanercept plus MTX groups. Comparisons between treatment arms showed that the rates of SAE for elderly subjects were numerically higher in the etanercept-treated group compared with the other treatment groups, whereas for younger subjects the SAE rate was numerically higher in the MTX group compared with the other treatment groups.

Although the rates of SAE tended to be higher in elderly than in younger subjects in the extension studies, rates within each age group did not exceed rates observed in the placebo group of the controlled LRA study or the MTX group of the controlled ERA study (Table 2A).

Rates of SIE were higher in elderly subjects in the controlled ERA and LRA studies, except for elderly subjects in the LRA trial who were treated with etanercept, in whom no infections were reported. Other comparisons between treatment groups showed similar rates of SIE within the controlled ERA and LRA studies. In TEMPO, the rates of SIE were similar between age groups and across treatment arms. Rates of SIE reported in the LRA and ERA extensions were similar to rates reported in either treatment arm of the respective controlled studies. For combined data from the ERA and LRA extensions, the 5 most frequent SIE were pneumonia, cellulitis, infection not otherwise specified, bacterial arthritis, and bronchitis.

Because of the short duration of the double-blinded trials,

Table 2A. Study drug exposure and event rates for SAE, SIE, and cancer in ERA and LRA subjects.

	Exposure to Study Drug, patient-years		SAE, Events per patient-year		SIE, Events per patient-year		Cancer*, Events per patient-year	
	PLA	Etanercept	PLA	Etanercept	PLA	Etanercept	PLA	Etanercept
LRA								
≥ age 65	5.9	8.6	0.510	0.116	0.680	0	0	0
< age 65	27.8	50.0	0.108	0.080	0.036	0.140	0.041	0
LRA extension								
≥ age 65	NA	475	NA	0.318	NA	0.099	NA	0.023
< age 65	NA	2629	NA	0.114	NA	0.030	NA	0.006
	MTX	Etanercept	MTX	Etanercept	MTX	Etanercept	MTX	Etanercept
ERA								
≥ age 65	41	52.9	0.417	0.321	0.074	0.095	0.049	0.057
< age 65	251	302	0.072	0.046	0.016	0.010	0.004	0.003
ERA extension								
≥ age 65	NA	303	NA	0.234	NA	0.069	NA	0.017
< age 65	NA	2004	NA	0.070	NA	0.018	NA	0.006

Sample sizes are given in Table 1. SAE: serious adverse event, SIE: serious infections episode, PLA: placebo, LRA: DMARD-resistant RA, MTX: methotrexate, ERA: early RA, NA: not applicable. * Does not include nonmelanomatous skin cancers.

Table 2B. Rates of serious adverse events (SAE), serious infectious episodes (SIE), and cancer in TEMPO subjects.

	Exposure to Study Drug, patient-years			SAE, Events per patient-year			SIE, Events per patient-year			Cancer*, Events per patient-year		
	MTX	ETN	MTX + ETN	MTX	ETN	MTX + ETN	MTX	ETN	MTX + ETN	MTX	ETN	MTX + ETN
TEMPO												
≥ age 65	37.5	41.7	37.3	0.240	0.360	0.242	0.080	0.096	0.054	0	0	0
< age 65	150	150	169	0.227	0.147	0.095	0.067	0.047	0.071	0	0.020	0

MTX: methotrexate, ETN: etanercept, TEMPO: Study of Etanercept and Methotrexate with Radiographic Patient Outcomes. * Does not include non-melanomatous skin cancers.

the relative rates of cancer were low and no consistent trends between age groups were identified (Table 2). In the extension studies, however, elderly subjects treated with etanercept had somewhat higher rates of cancer than younger subjects, although the number of cases of cancer observed in the extension studies was not different from the expected number in the general population, calculated from the SEER database. For the LRA extension, the number of cancers in elderly subjects was 11 observed versus 9.4 expected, and the number of cancers in younger subjects was 17 observed versus 18.3 expected. For the ERA extension, the number of cancers in elderly subjects was 5 events observed versus 6.1 cases expected, and the number of cancers in younger subjects was 12 observed versus 11.6 cases expected.

The number of lymphomas observed was higher than expected in the general population, except in elderly ERA subjects, where no lymphomas were reported. The number of lymphomas observed in elderly subjects in the LRA extension was 4 versus 0.37 cases expected, and the number observed in younger subjects was 3 versus 0.70 expected. In

the ERA extension, 2 lymphomas were observed in the younger subject group versus 0.47 expected.

No opportunistic infections were reported in elderly subjects in any of the studies. Four opportunistic infections were reported in younger subjects: candida cystitis (one case from the etanercept arm of the controlled ERA study and one from the ERA extension), gastrointestinal candidiasis (from the LRA extension), and varicella (from the etanercept plus MTX arm of TEMPO). No case of tuberculosis was reported.

Efficacy of etanercept assessed by ACR responses. ACR20 and ACR50 response rates for the controlled LRA and ERA studies and the extension studies are shown in Figure 1. In the controlled LRA study, ACR20 responses were about 10% to 26% in the placebo-treated subjects and 55% to 70% in the etanercept-treated subjects at the timepoints shown. The elderly etanercept-treated subjects had similar, or slightly lower, ACR responses compared with younger etanercept-treated subjects across all timepoints. ACR20/50/70 responses after 6 months of etanercept treatment were 70%/45%/15% for elderly subjects and 65%/39%/15% in

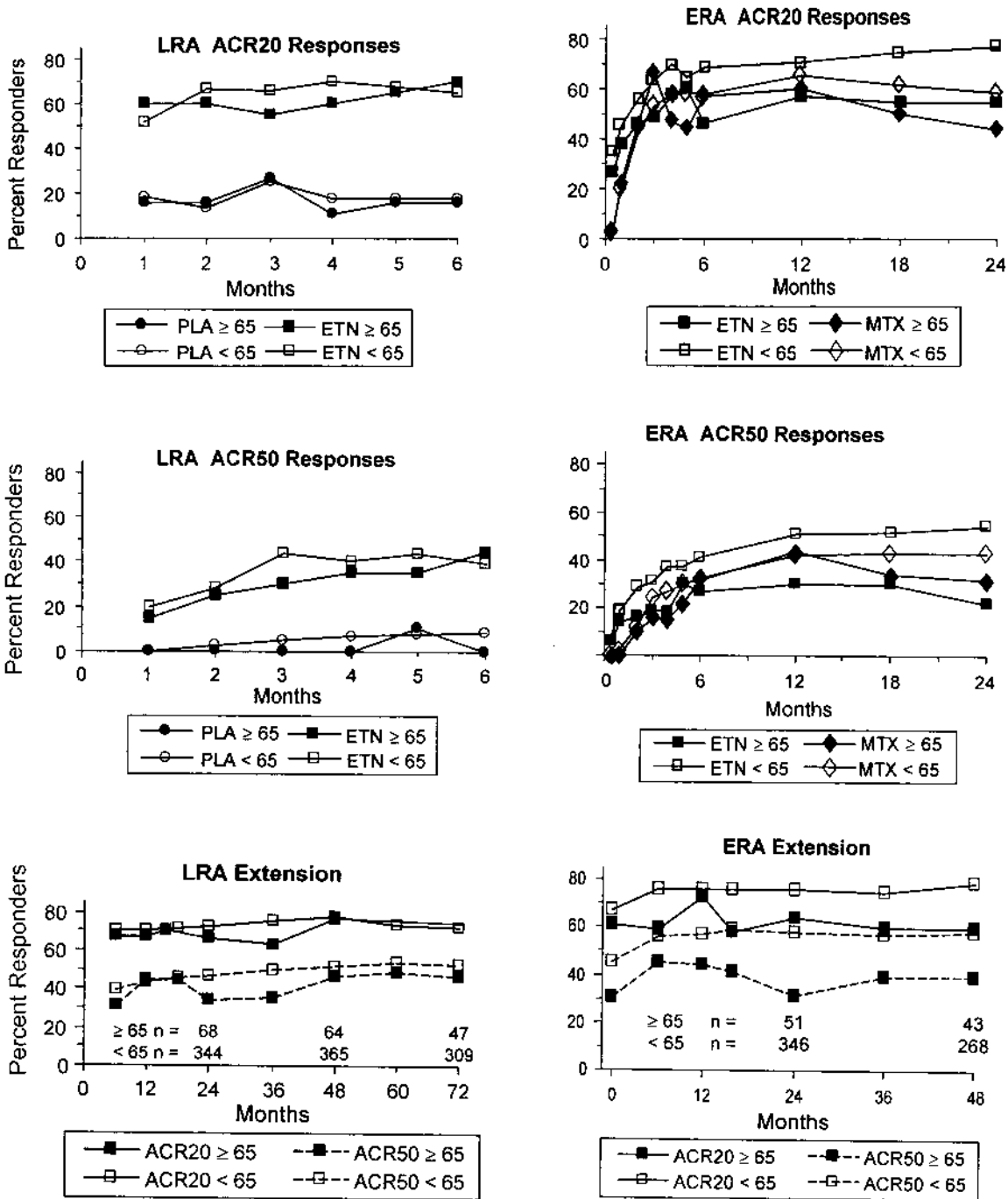


Figure 1. ACR scores over time in late-stage (LRA; left panels) and early RA (ERA; right panels) controlled and extension studies. Analysis of ACR responses was done using last observation carried forward. Sample sizes for the controlled studies are given in Table 1. Analysis of ACR responses for the extension studies is presented as "observed cases." For extension studies, timepoints are measured from baseline of the extension and do not include study drug exposure in the initial studies. Etanercept dosing was 25 mg twice weekly; all subjects in the extensions received etanercept. PLA: placebo, ETN: etanercept, MTX: methotrexate.

younger subjects. For the LRA extension, ACR responses were similar between the age groups; ACR20/50/70 responses were 70%/47%/11% in elderly subjects and 73%/53%/29% in younger subjects after 72 months of etanercept treatment in the extension.

In the controlled ERA study, ACR responses tended to be lower in the elderly group compared with the younger group in both the MTX and etanercept treatment arms. After 24 months of etanercept treatment, ACR20/50/70 responses were 54%/22%/14% for elderly ERA subjects and

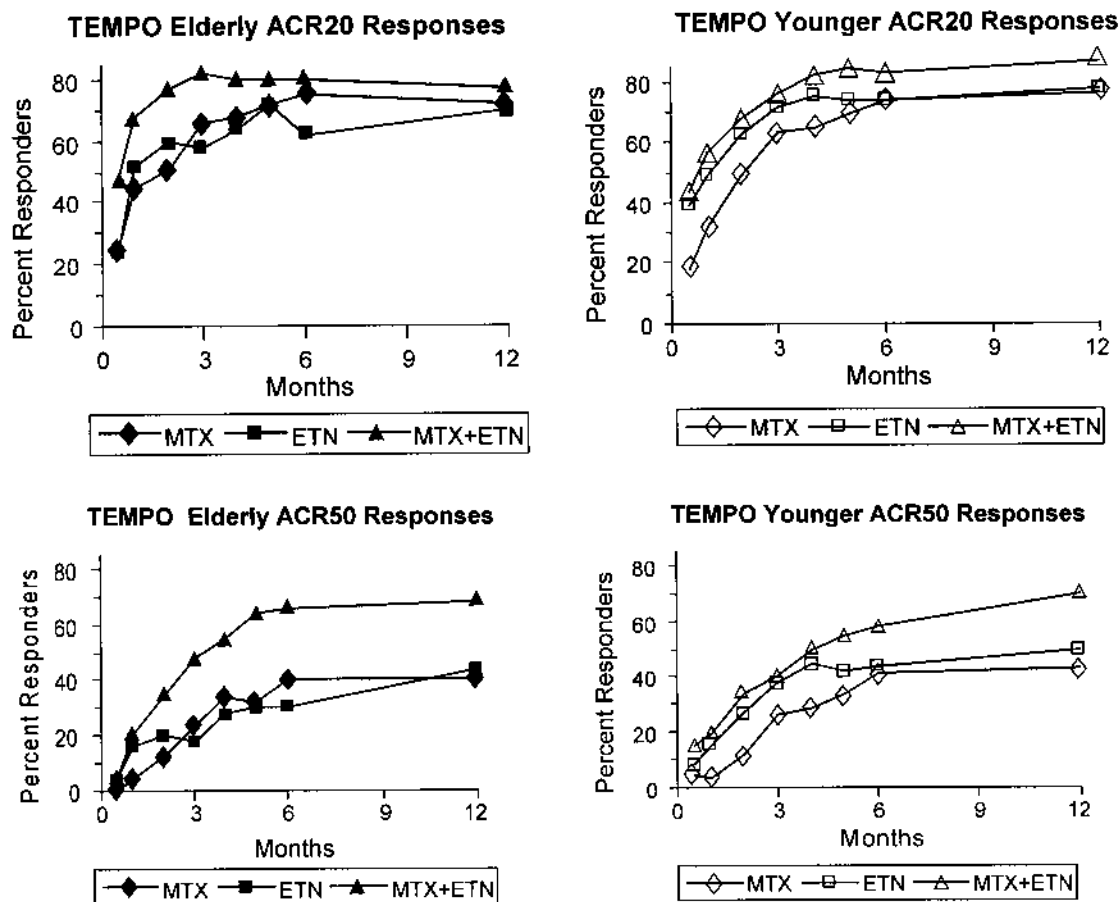


Figure 2. ACR scores over time in TEMPO. Sample sizes for TEMPO subject groups are given in Table 1. Analysis of ACR responses was done using last observation carried forward.

77%/54%/32% for younger subjects. Similarly, after 24 months of MTX treatment, the ACR20/50/70 responses were 44%/31%/13% for elderly subjects and 58%/43%/25% for younger subjects. In the ERA extension, ACR20/50/70 responses were 60%/40%/19% in elderly subjects and 79%/58%/40% in younger subjects after 48 months of treatment in the extension.

In the TEMPO study, ACR responses for subjects treated with etanercept plus MTX were higher than responses seen to either etanercept or MTX monotherapy (Figure 2). Interestingly, in elderly subjects there was a greater separation between the efficacy responses achieved with etanercept and MTX versus either monotherapy compared with the younger subjects (Figure 2). After 12 months of treatment with combination etanercept and MTX, ACR 20/50/70 responses were 77%/68%/39%.

Efficacy of etanercept in improving subject function. In general, clinically significant improvements in mean HAQ scores were observed with etanercept treatment during the controlled studies, and these improvements were sustained in the open-label studies (Figure 3). Overall, mean HAQ scores at baseline and at study endpoints tended to be high-

er (i.e., worse) in elderly subjects than in younger subjects. However, the changes in HAQ scores in response to etanercept treatment were similar in the 2 age groups.

In the controlled LRA study, the mean improvement from baseline in HAQ score for the elderly etanercept-treated group was 0.46 (SD 0.52) at Month 6, which is greater than the minimal clinically important difference (MCID) of 0.22. In contrast, the improvements were minimal in the elderly placebo group. In the LRA extension, the mean improvement from baseline in HAQ showed clinically significant improvement by Month 6 that was sustained through 72 months of treatment. The mean improvement from baseline in elderly subjects was 0.40 (SD 0.10), which is greater than the MCID.

Similarly, in the controlled ERA study the improvement in HAQ scores for elderly subjects showed improvement parallel to those of younger subjects, in both treatment arms. The mean improvement from baseline in HAQ scores of elderly subjects at 24 months was 0.61 (SD 0.78) for the elderly MTX-treated group and 0.46 (SD 0.66) for the elderly etanercept-treated group; both groups showed an improvement greater than the MCID. The same pattern occurred in

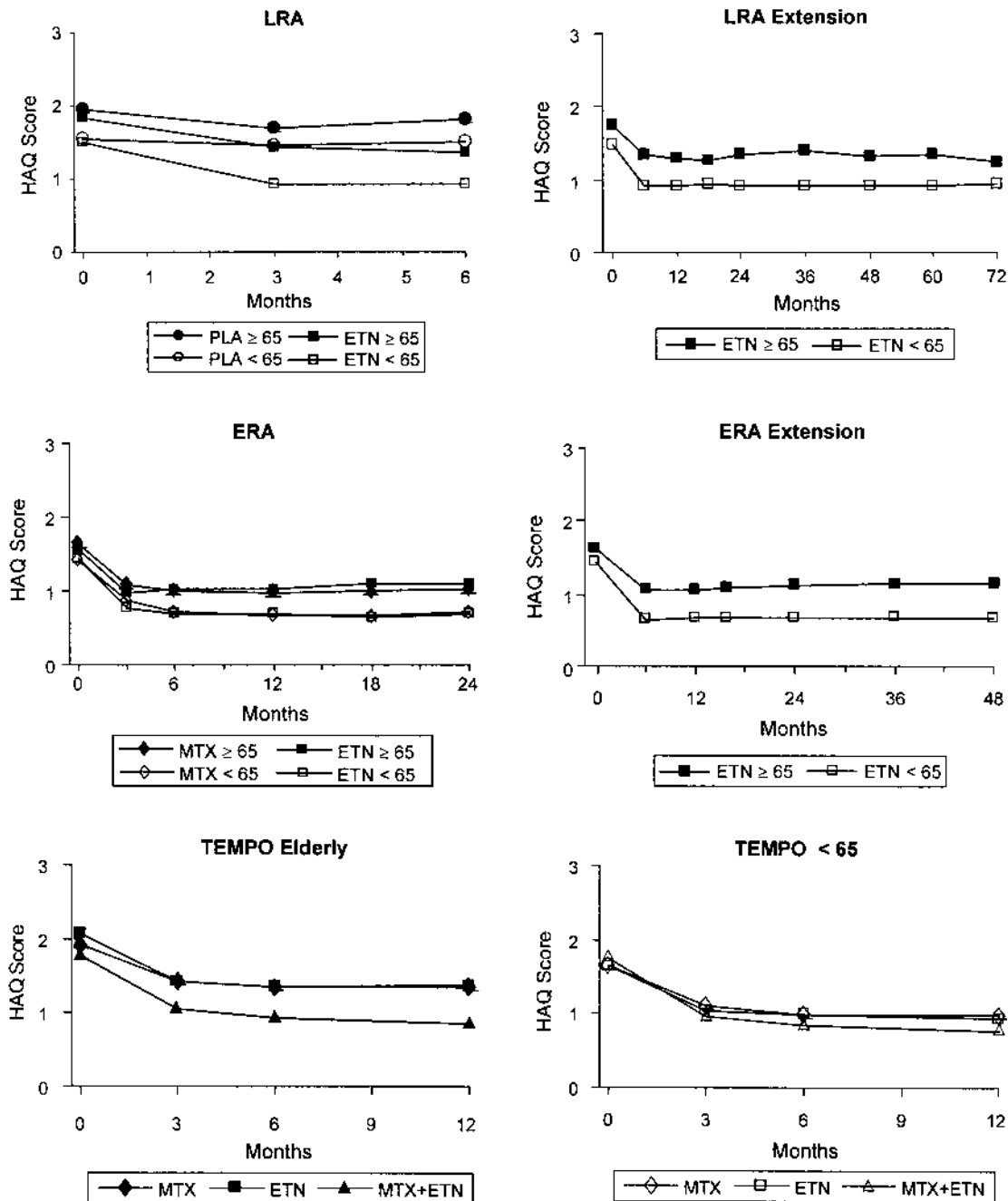


Figure 3. Health Assessment Questionnaire (HAQ) scores in controlled and extension studies. 0 = best, 3 = worst score. HAQ values are means. Analysis was done using last observation carried forward for the controlled studies and "observed cases" for the extensions. Sample sizes for the controlled trials are given in Table 2, and sample sizes for the extension studies are given in Figure 1. PLA: placebo, ETN: etanercept, MTX: methotrexate.

the ERA extension: mean HAQ scores showed clinically significant improvements by Month 6 that were sustained for 48 months. For elderly subjects, the mean change from baseline was 0.51 (SD 0.66) at Year 4, exceeding the MCID.

The TEMPO study showed a similar pattern, with the mean improvements from baseline in HAQ score exceeding the MCID in each of the 3 treatment groups. The mean improvement from baseline at 12 months for elderly sub-

jects was 0.57 (SD 0.63) for the MTX group, 0.71 (SD 0.78) for the etanercept group, and 0.92 (SD 0.70) for the etanercept plus MTX group. Similar degrees of improvement were seen in younger subjects, although elderly subjects appeared to derive greater functional benefit from combination therapy than monotherapy, while this difference was not observed in younger subjects.

Efficacy of etanercept in reducing progression of joint dam-

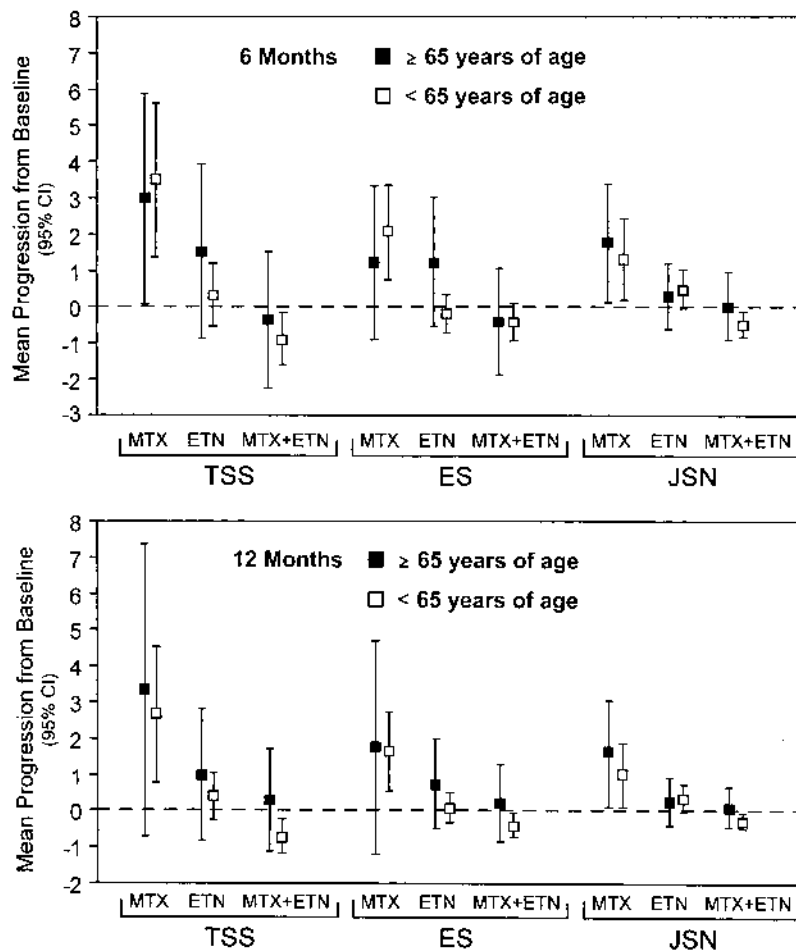


Figure 4. Mean progression from baseline in Total Sharp Score at 6 and 12 months for TEMPO subjects. Values are mean scores with 95% confidence intervals. Closed symbols represent data from subjects ≥ 65 years of age, open symbols represent subjects < 65 years of age. Sample sizes for groups are given in Table 1. MTX: methotrexate, ETN: etanercept, TSS: modified Total Sharp Score, ES: erosion score, JSN: joint space narrowing score.

age in RA. In the TEMPO study, radiographs were evaluated at baseline and after 6 and 12 months of therapy (Figure 4). Mean baseline absolute Total Sharp Score (TSS) values at baseline for elderly subjects were higher in all of the treatment groups compared with younger subjects. The mean TSS was 57 (SE 8.6) for elderly subjects in the MTX group, 55 (SE 8.0) for the etanercept group, and 57 (SE 9.8) for the etanercept plus MTX group. For the younger group, mean TSS at baseline was 46 (SE 4.5) for the MTX group, 41 (SE 4.8) for the etanercept group, and 41 (SE 3.7) for the etanercept plus MTX group.

Despite baseline differences, the patterns of response to treatments were similar in both age groups. Etanercept monotherapy was more effective in limiting progressive joint damage than MTX monotherapy at both 6 and 12 months in both age groups. Mean progression in TSS from baseline at 12 months was 3.4 (SE 2.0) Sharp units for elderly subjects treated with MTX monotherapy and 0.97 (SE

0.89) for etanercept-treated elderly subjects. The elderly etanercept plus MTX group showed the least progression from baseline in TSS compared with the other treatment groups, with the mean of 0.27 (SE 0.70). In younger subjects treated with combination etanercept and MTX, the mean progression from baseline was negative (-0.73, SE 0.24) and the 95% CI was below zero (-1.20, -0.25). With combination therapy, improvement in both joint space narrowing and erosions contributed to the low rate of progression in TSS (Figure 4).

DISCUSSION

The focus of our report is to describe the safety and efficacy of etanercept treatment in elderly and younger subjects and to examine the durability of the efficacy response with longterm etanercept treatment. Rates of SAE, SIE, and cancer tended to be slightly higher overall in the elderly group compared with the younger group. However, treatment with

etanercept did not increase the rates of SAE, SIE, or cancer observed in the controlled studies in either age group, compared with the control arms (either placebo or MTX). This suggests that treatment with etanercept does not increase the risk of these events in the elderly population beyond the increases inherent with advanced age and comorbidities. Only 4 opportunistic infections and no cases of tuberculosis were reported during the 5815 patient-years of etanercept exposure in these clinical studies.

Although elderly subjects overall had somewhat less robust responses to treatment than younger subjects, the patterns of response were similar in the 2 age groups. In the LRA studies, subjects in both age groups who received etanercept had higher ACR responses and disease activity scores (data not shown) than subjects receiving placebo. In TEMPO, subjects in both age groups exhibited superior ACR and HAQ responses to combination therapy with etanercept plus MTX, compared with either etanercept or MTX monotherapy. In addition, combination therapy was more effective in reducing joint damage in both age groups, especially when compared with MTX monotherapy. This result is similar to results obtained in a study that included elderly subjects receiving adalimumab plus MTX¹⁹. In a subanalysis of elderly subjects from this study, the mean change from baseline in TSS observed after 12 months of therapy was 3.2 (SD 5.5) for subjects treated with MTX monotherapy and 1.6 (SD 4.8) for subjects treated with adalimumab plus MTX. Thus, less progression of joint damage may occur when elderly patients are treated with a combination of a TNF inhibitor plus MTX than with MTX alone.

The efficacy results observed in the controlled studies are extended by the longterm results from the extension studies presented here. Treatment with etanercept resulted in durable clinical responses for up to 6 years of open-label treatment with etanercept in LRA subjects (Figure 1). Similarly, ERA subjects showed durable clinical responses not only during 2 years of treatment with either MTX or etanercept in the controlled study, but also during an additional 4 years of open-label treatment with etanercept in the extension (Figure 1).

Functionality, measured by HAQ scores, was improved in elderly subjects treated with etanercept. Elderly subjects tended to have higher HAQ scores at baseline and study endpoints than younger subjects in the controlled studies and the extensions. Nonetheless, their HAQ scores improved with etanercept treatment either as monotherapy or in combination with MTX. A report by Schiff, *et al*²⁰ describes the HAQ responses of these subjects in greater depth. The ability to improve function in the elderly with etanercept treatment, especially combination therapy, may be an important consideration in elderly patients with RA.

A limitation of this post-hoc analysis is that longterm efficacy results are based on a select group of subjects who remained in the study (data are "as observed" case analyses).

Efficacy results reported for the extensions may be higher than expected for the general population of elderly patients with RA, since subjects who did not respond to etanercept treatment may be more likely to discontinue. Similarly, safety events may underestimate those in the general RA patient population, if the study subjects have less comorbidity.

It may be difficult to generalize these findings to the entire RA patient population. Clinical trials in RA usually select subjects with moderate to severe RA who do not have significant comorbidities. Overall, elderly subjects in these studies may be healthier than elderly RA patients in the general population. Whether the safety profile and efficacy results of etanercept observed in elderly RA subjects in clinical trials extend to the general population of elderly RA patients remains to be determined.

Etanercept therapy was safely continued for up to a total of 6 years in the elderly RA subjects studied in these clinical trials. No substantial differences were apparent in the rates of SAE, SIE, cancer, or lymphoma between elderly subjects receiving etanercept and elderly subjects receiving placebo or MTX. Elderly RA subjects treated with etanercept experienced rapid clinical improvement in controlled clinical studies and durable clinical responses that were sustained for a total of up to 6 years. In subjects with early or DMARD-refractory RA, consistent, sustained improvement in signs and symptoms, efficacy, and physical function was seen in the majority of elderly subjects. In both elderly and younger subjects, efficacy responses, including functionality, showed sustained improvement and the rate of progression of joint damage was reduced.

ACKNOWLEDGMENT

The authors thank the many clinical investigators and study coordinators who participated in these studies. Also, the authors thank Susan Myers, MSc, for her assistance in drafting the manuscript.

REFERENCES

1. Hochberg MC. Predicting the prognosis of patients with rheumatoid arthritis: is there a crystal ball? *J Rheumatol* 1993;20:1265-7.
2. Bazzoni F, Beutler, B. The tumor necrosis factor ligand and receptor families. *N Engl J Med* 1996;334:1717-25.
3. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999;340:253-9.
4. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med* 1999;130:478-86.
5. Lipsky PE, van der Heijde DM, St. Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000;343:1594-602.
6. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;343:1586-93.
7. Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002;46:1443-50.

8. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy. A randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004;50:1400-11.
9. Klareskog L, van der Heijde DM, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004;363:675-81.
10. Mitchell D. Epidemiology. In: Utsinger PD, Zvaifler NJ, Erlich GE, editors. *Rheumatoid arthritis: etiology, diagnosis, management*. Philadelphia: Lippincott; 1985:1333-73.
11. Robinson H. Multidisciplinary ambulatory care for the elderly arthritis patient. In: Moskowitz RW, Haug MR, editors. *Arthritis and the elderly*. New York: Springer Publishing; 1986:146-9.
12. Terkeltaub RJ, Esdaile J, Deccary F, Tannenbaum H. A clinical study of older age rheumatoid arthritis with comparison to a younger onset group. *J Rheumatol* 1983;10:418-24.
13. Papadopoulos IA, Katsimbri P, Alamanos Y, Voulagari PV, Drosos AA. Early rheumatoid arthritis patients: relationship of age. *Rheumatol Int* 2003;23:70-4.
14. Fleischmann RM, Baumgartner SW, Tindall EA, et al. Response to etanercept (Enbrel) in elderly patients with rheumatoid arthritis: a retrospective analysis of clinical trial results. *J Rheumatol* 2003;30:691-6.
15. Center for Drug Evaluation and Research. Coding symbols for a thesaurus of adverse reactions terms. 3rd ed. Washington, DC: US Department of Health and Human Services; 1990.
16. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program Public-Use Data (1973-1999). DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2002, based on the November 2001 submission. Bethesda, MD: National Cancer Institute; 2002.
17. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum* 1993;36:729-40.
18. van der Heijde DM, van Riel PL, Nuver Zwart IH, Gribnau FW, van de Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet* 1989;1:1036-8.
19. US Food and Drug Administration, Center for Drug Evaluation and Research, Product Approval Information – Licensing Action. Clinical Review, Adalimumab — for use in the treatment of rheumatoid arthritis, Humira, Abbott, Biologic Licensing Application, STN 125057. Approved: December 31, 2003. Internet. Available from: <http://www.fda.gov/cder/biologics/review/adalabb123102r1.htm>. Accessed October 7, 2005.
20. Schiff MH, Yu EB, Weinblatt ME, et al. Long-term experience with etanercept in the treatment of rheumatoid arthritis in elderly and younger patients: Patient-reported outcomes from multiple controlled and open-label extension studies. *Drugs and Aging* 2006; (in press).