Response to Etanercept (Enbrel®) in Elderly Patients with Rheumatoid Arthritis: A Retrospective Analysis of Clinical Trial Results

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ABSTRACT. ***Objective***. Approximately 3% of the US population over the age of 65 years has rheumatoid arthritis (RA). We compared the safety and efficacy of etanercept (Enbrel®) in patients with RA who were ≥ 65 years to those < 65 years in open-label and double-blind, randomized clinical trials.

Methods. Patients from 4 double-blind, randomized controlled trials and 5 open-label trials were included in this retrospective analysis. Patients were grouped by age (< 65 or ≥ 65 yrs) at time of study entry. All patients received etanercept subcutaneously twice weekly. Improvement in signs and symptoms was assessed by the proportion of patients who achieved the American College of Rheumatology definition of improvement (ACR 20). The ACR 50 and ACR 70 responses were calculated in an analogous fashion. Safety was assessed at regularly scheduled visits.

Results. Of 1128 patients enrolled in etanercept trials, 197 (17%) were ≥ 65 years of age. Clinical response was rapid and sustained and did not differ between age groups. At one year, 69% of patients < 65 years and 66% of patients ≥ 65 years met the ACR 20. Forty percent of the patients ≥ 65 years met the ACR 50 and 17% met the ACR 70. Etanercept was well tolerated. Although injection site reactions, headache, and rhinitis occurred somewhat more frequently in younger patients, the overall rates and types of other adverse events were comparable in both groups.

Conclusion. Etanercept is a new treatment option for older patients with RA and has substantial benefit and comparable safety regardless of patient age. (J Rheumatol 2003;30:691–6)

Key Indexing Terms:
ETANERCEPT
ELDERLY
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Disorders of the musculoskeletal system have a major impact on quality of life and on the use of health care resources in patients over the age of 65[1-3]. Significant among these is rheumatoid arthritis (RA), a chronic inflammatory disorder that causes significant morbidity. It occurs in approximately 1% of the US population, but is more prevalent in patients older than 65 years[4,5]. Although RA is most commonly diagnosed during the third to fifth decades of life, 10–33% of patients are diagnosed after the age of 60[5-11]. In one study, the mean age of patients diagnosed with RA was 58 years, an increase of 7.6 years in the average age of diagnosis reported in the same population 15 years earlier[12]. The joint destruction and systemic inflammation that is characteristic of RA may have a greater effect on elderly patients due to the presence of other comorbid conditions that adversely affect their quality of life[13].

Despite the high prevalence of RA in the elderly, and the likelihood that older patients have adverse reactions to medications as a result of age-related changes in drug metabolism and the presence of comorbid illnesses requiring concomitant medications, patients older than 65 years tend to be inadequately represented in RA clinical trials[14,15]. Also, the tolerability of and response to therapy in these patients as a group has not been studied in detail. In one retrospective analysis of disease modifying antirheumatic drugs (DMARD) including gold, D-penicillamine, azathioprine, and methotrexate (MTX), a substantially higher withdrawal rate due to toxicity was observed in

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patients older than 65 years compared to those younger than 65 years[14].

Etanercept is a recombinant human fusion protein that inhibits the activity of tumor necrosis factor and lymphotoxin-α. In clinical trials of RA, etanercept alone or in combination with MTX was well tolerated and produced significant sustained improvement in disease activity in patients with long-standing RA who failed multiple DMARD and in patients with early aggressive disease who never received MTX[16-19]. Etanercept is effective in inhibiting radiographic progression in patients with RA; 72% of patients with early aggressive RA who received 25 mg etanercept monotherapy had no new radiographic erosions during one year of treatment[19]. In these clinical trials, the response to etanercept therapy in elderly patients was not described in detail. To evaluate the response in this elderly population with RA, we retrospectively compared the safety and efficacy results of etanercept in patients ≥ 65 years to those of patients < 65 years of age.

MATERIALS AND METHODS

Patients from 4 double-blind, randomized controlled trials and 5 open-label trials were included in this retrospective analysis. Eight trials evaluated patients with long-standing disease who failed previous DMARD therapy, and one trial evaluated patients with recent-onset RA (≤ 3 yrs) who never received MTX[16-19]. Patients with RA were grouped by age (< 65 or ≥ 65 yrs) at study entry. All patients received etanercept subcutaneously twice weekly.

Statistical analysis. Efficacy was assessed by completer analysis, where patients who discontinued etanercept before receiving one year of treatment were excluded from efficacy evaluations subsequent to their withdrawal. Improvement in signs and symptoms was assessed in patients who were eligible to receive etanercept continuously for at least one year. Improvement criteria were the proportion of patients who achieved the American College of Rheumatology (ACR) definition of improvement (ACR 20) and changes in the individual components of the response criteria. The ACR 20 is defined as a minimum 20% improvement in tender and swollen joint counts and a minimum 20% improvement in 3 of the 5 remaining ACR core set measures: patient and physician global assessments, pain, disability, and an acute phase reactant[20]. The ACR 50 and ACR 70 responses were calculated in an analogous fashion. Safety in all patients who received etanercept was assessed at regularly scheduled visits by physical examinations, hematology and chemistry profiles, and urinalyses.

Event rates were calculated as number of events per patient-year receiving therapy to account for varying time taking etanercept. Differences in simple proportions of events were assessed by standard chi-square test. Differences between groups in event rates were assessed by the exact binomial test[21]. The observed rate of malignancies was compared to the age- and sex-adjusted rate predicted by the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database[22].

RESULTS

Patient population. This retrospective analysis included 1128 patients: 931 (83%) were < 65 and 197 (17%) were ≥ 65 years of age. Of the 931 patients < 65 years, 582 had advanced RA, and 43 patients with advanced RA had disease duration of less than 3 years. Of 197 patients aged ≥ 65 years, 131 had advanced RA and 66 had early RA. Six patients with advanced RA had disease duration of less than 3 years. Table 1 shows that demographic distribution was comparable in the 2 groups. The number of patients with advanced RA who failed at least one DMARD was similar in each age group as was the number of patients with early RA who never received MTX.

Efficacy. Efficacy was assessed in 875 patients < 65 years of age and in 184 patients ≥ 65 years who were eligible to receive etanercept continuously for at least one year. ACR 20 responses during the first year of etanercept treatment are shown in Figure 1. Responses were rapid and sustained in both groups. A similar proportion of patients in both age groups met the ACR 20 at various time points during the year. At 3 months, 61% of patients < 65 years and 55% of patients ≥ 65 years met the ACR 20 ($p = 0.163$). At one year, 69% of patients < 65 years and 66% of patients ≥ 65 years met the ACR 20 ($p = 0.480$). Similar proportions of patients in the 2 age groups met the ACR 50 (44% of patients < 65 yrs and 40% of patients ≥ 65 yrs) and the ACR 70 (20% of patients < 65 yrs and 17% of patients ≥ 65 yrs) at one year. The proportions of patients with early RA who achieved an ACR 20 response were similar in those < 65 years of age and those ≥ 65 years (58% vs 51%; $p = 0.265$). Findings were comparable in patients with late RA, whether they were under 65 years of age or over that age (63% vs 58%; $p = 0.321$). The placebo response rates in previously reported controlled trials in patients with DMARD-failing RA were 24% (patients < 65 yrs) and 17% (patients ≥ 65 yrs) at 3 months, and 12% (patients < 65 yrs) and 8% (patients ≥ 65 yrs) at 6 months[23]. Treatment with etanercept also provided rapid and significant improvement in the number of tender and swollen joints in both groups (Figure 2).

Adverse events. Table 2 shows the rate (events per patient-year where one patient-year represents one year of observation) and frequency of adverse events reported by 10% of patients in either age group. The 931 patients < 65 years

Table 1. Demographic and baseline information.

	Age Group	
	< 65 years, n = 931	≥ 65 years, n = 197
Early RA*, n (%)	349 (37)	66 (34)
Advanced RA† n (%)	582 (63)	131 (66)
RA duration		
Early RA, mean (median)	1.0 (0.7)	0.9 (0.7)
Advanced RA, mean (median)	12 (10)	14 (11)
Mean (median) age in years	48 (49)	70 (70)
Range	(18–64)	(65–86)
Females, %	78	74
Race, %		
Caucasian	87	94
Black	4	0
Other	9	6

*Defined as disease duration of ≤ 3 yrs. †Defined as having failed one or more DMARD.

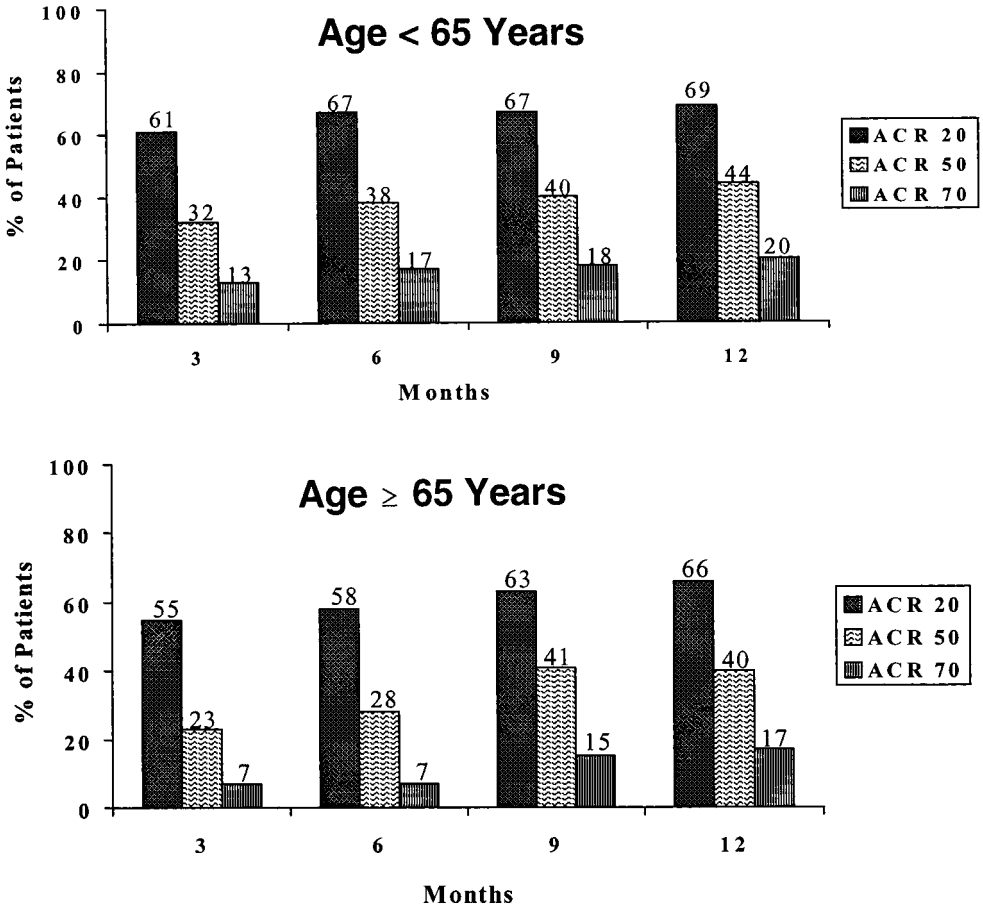

Figure 1. Proportion of patients by age group who achieved ACR 20%, ACR 50%, and ACR 70% response during the first year of therapy.

were observed for 1010 patient-years, while the 197 patients ≥ 65 years were observed for 194 patient-years. Treatment with etanercept was well tolerated. Most adverse events were mild and occurred with a similar frequency in the 2 groups, although injection site reactions, headache, and rhinitis occurred statistically more frequently among patients in the younger age group.

Medically important infections (associated with hospitalization or intravenous antibiotic treatment) were uncommon, occurring in 31 (3%) of 931 patients < 65 years and in 14 (7%) of 197 patients ≥ 65 years. Although adjusted for time of observation, these infections were more common in older than younger patients (0.09 vs 0.04 events/patient-year; p = 0.003). Thirteen of the 14 older patients who developed a medically important infection continued treatment with etanercept.

Five patients who were ≥ 65 years of age died, one each due to accidental injury, cardiac arrest, lung cancer, ovarian cancer, and infection. Based on estimates from an age- and sex-adjusted population, the expected number of deaths for a population of this size for patients ≥ 65 years is 6.5[24]. Three patients who were < 65 years died, one each due to lung cancer, myocardial infarction, and aortic aneurysm.

Nine patients < 65 years of age were diagnosed with cancers, including breast (2), lung (2), and ovarian cancer (2); adenocarcinoma of the common bile duct (1); Hodgkin's disease (1); and non-Hodgkin's lymphoma of the parotid (1). Of 5 patients ≥ 65 years who were diagnosed with cancer, 2 had prostate cancer, 2 had lung cancer, and one had Hodgkin's disease. The age-adjusted rates predicted from the SEER database are 8.4 cancers among patients < 65 years and 5.5 among those ≥ 65 years[22].

DISCUSSION

This retrospective analysis showed that etanercept was effective in the treatment of RA in patients of all ages, with more than 60% of patients in both age groups achieving an ACR 20 at 12 months. The clinical response to etanercept was rapid and sustained. There were no consistent differences in the rates or types of adverse events and no evidence of cumulative toxicity with continued use. Etanercept was well tolerated in both age groups. Previous studies have shown that the pharmacokinetics of etanercept do not change with age[25].

Rheumatoid arthritis is a major cause of disability and institutionalization in an aging population[26]. The joint pain

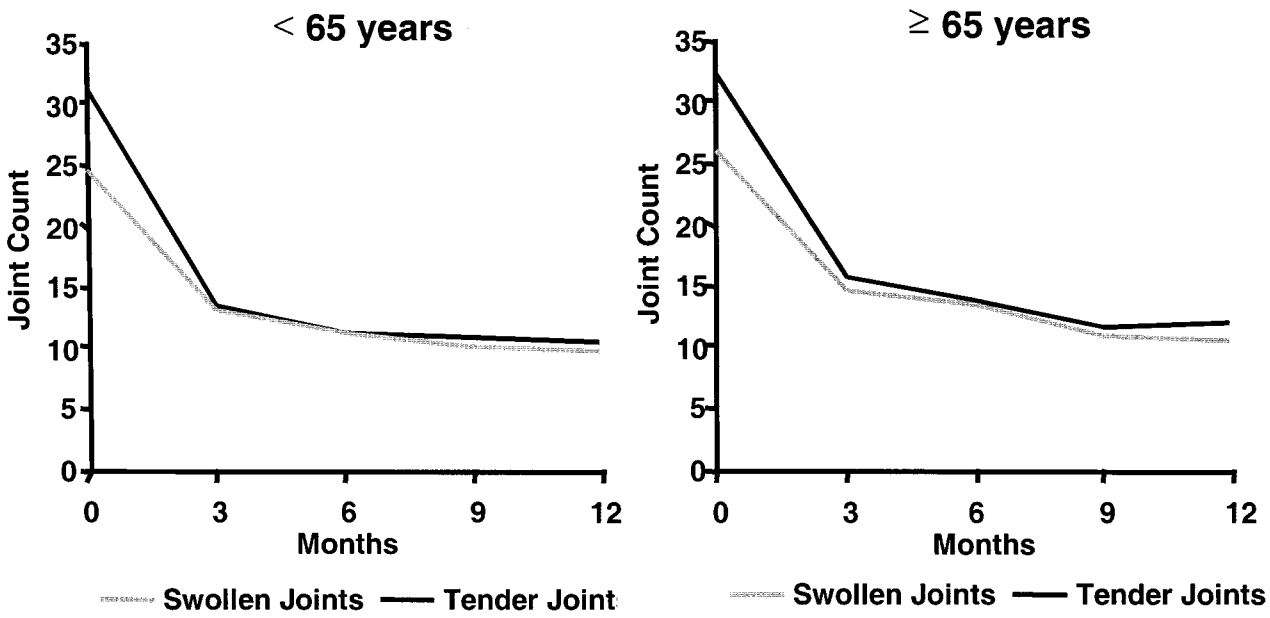

Figure 2. Improvement in swollen and tender joints by age group during the first year of therapy.

Table 2. Rate (events/patient-year) and frequency (%) of adverse events seen in ≥ 10% of patients.

	Rate			Frequency		
	< 65 years (n = 931)	≥ 65 years (n = 197)		< 65 years (n = 931)	≥ 65 years (n = 197)	
Patient-years	1010	194	p*	%	%	p†
Adverse Events						
Any infection	1.56	1.36	0.036	68	64	NS
Injection site reaction	4.31	1.47	< 0.001	42	28	< 0.001
Rash	0.17	0.21	NS	14	16	NS
Diarrhea	0.16	0.18	NS	12	14	NS
Headache	0.37	0.18	< 0.001	24	11	< 0.001
Nausea	0.19	0.18	NS	15	13	NS
Abdominal pain	0.10	0.14	NS	10	10	NS
Rhinitis	0.19	0.10	0.006	17	9	0.011

*Exact binomial test.†Chi-square test.

and swelling that is characteristic of RA often impairs mobility and the performance of activities of daily living, resulting in difficulties in self-care, diminished independence, and reduced involvement in family, work, and social roles[27,28]. The influence on functional status is especially critical in older patients with RA, who also tend to have a higher frequency of acute onset and weight loss at presentation and are more likely than younger patients to have large joint involvement[15,29]. Some studies have suggested that in the elderly, RA is more aggressive, is associated with more radiographic damage, and may result in more rapid functional decline than in younger patients[30-32].

Special issues confound the choice of therapy for elderly patients. Older patients in general are more likely to have concomitant illness, including malignancies and cardiovascular disease. Additionally, they are more susceptible to serious infections and mortality from infections[33]. Medication compliance, drug interactions, and decreased tolerability complicate the management of older patients. The older patient with RA is likely to require multiple medications and have difficulties with drug compliance, and may be prone to commit dosage errors. Physiological factors in the elderly may modify pharmacokinetics, tissue responsiveness, and homeostatic mechanisms[34].

These factors may contribute to differences in toxicity and efficacy among different age groups in patients with RA[15]. Nonsteroidal antiinflammatory drugs pose high risks for older patients with respect to both renal and gastrointestinal toxicity. Among DMARD, hydroxychloroquine is among the least toxic, but maculopathy is of special concern

in the elderly[35-37]. Sulfasalazine appears to be comparably effective in all age groups, but a greater number of elderly patients discontinue treatment mainly because of gastrointestinal adverse effects[35,38]. MTX, the most frequently prescribed of the DMARD, has adverse effects that are seen more commonly in the elderly and can lead to discontinuation of treatment. These adverse effects include oral ulcers, gastrointestinal symptoms, alopecia, bone marrow suppression, and hepatotoxicity[32]. Given the higher frequency of these adverse events in the elderly and the trend toward use of combination therapy in the treatment of RA, the use of etanercept as monotherapy is a definite advantage over other treatments in this population.

This study is the first to report the response to a biologic agent in an older RA population. As a targeted DMARD, etanercept is safe and well tolerated in this subset of patients. Unlike reports of other DMARD therapies in the elderly, there is no increased or cumulative toxicity with etanercept. It offers older patients with RA a rapid, predictable, and sustained clinical response, and is a significant addition to treatment options for these patients.

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