EXTENDED REPORT

Long term safety of etanercept in elderly subjects with rheumatic diseases

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Ann Rheum Dis 2006;**65**:379–384. doi: 10.1136/ard.2005.035287

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Accepted 27 August 2005
Published Online First 8 September 2005

Objectives: To determine the long term safety profile of the tumour necrosis factor (TNF) antagonist etanercept in subjects with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) aged ⩾65 years in comparison with subjects aged <65 years.
Methods: Safety data from an integrated database of 4322 subjects enrolled in 18 RA trials, 2 PsA trials, and 2 AS trials were analysed. Safety end points included subject incidence of all adverse events (AE), serious adverse events (SAE), infectious events (IE), medically important infections (MII), and deaths. Events of particular interest in subjects treated with TNF modulating biological treatments, including demyelinating diseases, tuberculosis, lymphomas, and cardiovascular diseases, were also evaluated.
Results: The incidence of AE, SAE, IE, MII, and malignancies was not significantly raised in elderly subjects in comparison with subjects aged <65 years. No cases of tuberculosis were reported in the trials. Demyelinating diseases were seen only in subjects aged <65 years. The incidence and types of death in the elderly subjects were consistent with the expected rates for subjects of comparable age.
Conclusions: Etanercept is a generally safe and well tolerated biological agent for treatment of rheumatological diseases in the elderly, and the risk of AE in these studies was no greater in subjects aged ⩾65 years than in younger subjects.

Epidemiological studies have indicated that the incidence of rheumatoid arthritis (RA) increases with age, reaching an annual rate of about 130 cases per 100 000 population for women over the age of 65 in the United States.[1] Despite the high incidence of this disease in the elderly, patients who are ⩾65 years of age have been consistently underrepresented in clinical trials of arthritis treatments.[2] Older patients tend to present with more severe disease than younger subjects,[3] and advancing age is a predictor of poor radiographic outcome[4] and risk of permanent work disability.[5] In contrast with RA, the age of onset of subjects with inflammatory spondyloarthritides, which include psoriatic arthritis (PsA) and ankylosing spondylitis (AS), is generally under the age of 40.[6] However, elderly subjects with PsA tend to present with a more severe onset of disease than younger subjects, and have a more destructive outcome.[7] Similarly, subjects with late onset AS are more likely to present with systemic symptoms, inflammatory upper spinal pain, and peripheral arthritis than younger subjects.[8] In general, older subjects also present with a greater number of comorbidities, resulting in higher levels of polypharmacy and increased risk of adverse pharmaceutical interactions. Older people therefore represent a rapidly growing population of rheumatology patients with unique challenges, requiring special considerations to achieve desirable clinical outcomes safely.

Many rheumatic diseases, including RA, PsA, and AS, are autoimmune conditions, characterised by dysregulation and chronic activation of T cell responses.[9 10] The ultimate outcome is the overproduction of proinflammatory cytokines, including tumour necrosis factor (TNF) and interleukin 1, which have been postulated to mediate the joint destruction seen in RA.[11 12] TNF blockade is currently the most effective biological approach to the treatment of RA, with demonstrated efficacy and safety.[12 13] Etanercept is a fully human, soluble, TNF receptor-IgG1 fusion protein that binds to both soluble and membrane bound TNF, thereby inhibiting its interaction with cell surface receptors and preventing TNF mediated cellular responses. Etanercept has been approved by the Federal Drug Administration for the treatment of subjects with moderately to severely active RA, PsA, polyarticular juvenile RA (JRA), AS, and psoriasis.[14] Long term extension studies in subjects with RA have been performed for up to 7 years.[15] In addition, more than 262 000 patients have been treated with etanercept outside clinical trials world wide, representing over 515 000 patient-years of experience.

This study aimed at determining the incidence of important adverse reactions in a database of subjects with RA, PsA, and AS enrolled in clinical trials who were 65 years of age and older and contrasting the results with the incidence of adverse events reported in subjects under the age of 65 years who were taking etanercept. Although subjects in clinical trials are carefully screened for the absence of multiple, clinically significant comorbidities, this database should suggest whether such older subjects are more likely to have significant adverse events than younger patients when treated with etanercept.

SUBJECTS AND METHODS

Subjects

Subjects with active rheumatic diseases enrolled in all clinical trials performed to evaluate the safety and efficacy of etanercept in the treatment of RA (18 trials), PsA (2 trials), and AS (2 trials) were included. Safety data were collected from all subjects who had received at least one dose of etanercept, and pooled for this integrated analysis. Safety data for patients receiving etanercept who are not in clinical

Abbreviations: AE, adverse events; AS, ankylosing spondylitis; CHF, congestive heart failure; IE, infectious events; JRA, juvenile rheumatoid arthritis; MII, medically important infections; MTX, methotrexate; OR, odds ratio; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SAE, serious adverse events; SIR, standardised incidence ratio(s); TNF, tumour necrosis factor

Table 1 Subject demographics at baseline in all studies

Characteristics	RA		PsA		AS	
	Age <65 (n = 2772)	Age ≥65 (n = 579)	Age <65 (n = 251)	Age ≥65 (n = 14)	Age <65 (n = 273)	Age ≥65 (n = 4)
% of total subjects in group	82.7	17.3	94.7	5.3	98.6	1.4
Sex, No (% female)	2134 (77.0)	424 (73.2)	116 (46.2)	10 (71.4)	67 (24.5)	0 (0.0)
Race, No (% white)	2180 (78.6)	518 (89.5)	224 (89.2)	14 (100.0)	253 (92.7)	4 (100.0)
Age (years)						
Median	47	70	46	70	42	65
Range	1–64	65–90	18–64	65–76	18–64	65–70

RA, rheumatoid arthritis; PsA, psoriatic arthritis; AS, ankylosing spondylitis.

trials are not systematically collected, and therefore are not included in this analysis.

Study designs

RA trials

Subjects were enrolled in one phase I trial,[16] one phase II trial,[17] two phase II/III trials,[18 19] four phase III trials,[20–22] one phase IV trial, two pharmacokinetic studies,[23] four open label trials,[24 25] one investigator initiated trial, and two trials designed to examine the safety and efficacy of lyophilised and liquid[26] formulations of etanercept were included in this safety analysis. All the trials enrolled subjects with moderate to severe RA, and two of the trials examined only subjects with JRA.[19]

PsA trials

Subjects with PsA who had both skin and joint symptoms were enrolled in two clinical trials designed to examine the safety and efficacy of etanercept in the treatment of PsA symptoms.[27 28]

AS trials

Subjects with moderate to severe AS who were enrolled in a randomised, placebo controlled trial[29] and an open label extension of that trial[30] were included in this safety analysis.

Study drug

Etanercept (Enbrel; Immunex-Wyeth Research) was supplied to subjects in syringes, each containing the contents of one reconstituted vial of etanercept or placebo. The study drug was self administered by subcutaneous injection. In some studies, subjects were initially given reconstituted drug, and were later given vials to be reconstituted at home.

Safety end points

The integrated dataset used to evaluate safety included data from all subjects who received at least one dose of etanercept in Amgen sponsored studies (completed and continuing) in approved rheumatological indications through 31 December 2003. Safety end points included subject incidence rates of all adverse events (AE), serious adverse events (SAE), infectious events (IE), medically important infections (MII), and deaths. MII are defined as infections that required the use of intravenous antibiotics or admission to hospital. The reporting of MII was chosen for this analysis in order to capture infections that are of clinical interest, rather than serious IE, which is a regulatory definition and may under-report clinically relevant events.

AE that are of particular interest in TNF modulating biological treatments, including tuberculosis, demyelinating disorders, and cardiovascular diseases, were also evaluated. Assignment of the term congestive heart failure (CHF) included the following preferred terms that could represent CHF: CHF, aggravated CHF, oedema lung, effusion pleural, fluid overload, heart failure, right heart failure, and peripheral oedema. Preferred terms used to identify potential cases of demyelinating disorders included paraesthesia, multiple sclerosis, optic neuritis, and neuropathy. All AE were classified using the current Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) dictionary for each trial except for the trial of the liquid formulation of etanercept, which used the Medical Dictionary for Drug Regulatory Affairs (MedDRA) coding. Intensities of AE were classified according to a modified National Cancer Institute Common Toxicity Criteria Scale.

Table 2 Subject-years of exposure to etanercept

	Age	
	<65 Years	≥65 Years
RA	5592	887
PsA	245	15
AS	58	1
Total	5895	903

RA, rheumatoid arthritis; PsA, psoriatic arthritis; AS, ankylosing spondylitis.

Statistical methods

The purpose of these integrated safety analyses was to explore various profiles of AE during exposure to etanercept, and to compare AE in elderly subjects aged ≥65 and subjects aged <65. Subjects from the 22 rheumatology trials were divided into two cohorts: those aged ≥65 years and those aged <65, where age is calculated relative to the date a subject first received etanercept. Within each age cohort, the subject incidence of events that occurred during exposure to etanercept (including treatment during the initial randomised trials and up to 5 years in extension studies) and during the control period are summarised. The incidence of treatment related events was determined by subtracting event rates in the control groups from event rates in the treated groups. Differences between incidence in the etanercept treatment group and the control group are reported with 95% confidence intervals (CIs). No differences were found in the incidence of most AE between subjects aged <65 and subjects aged ≥65, and no major differences in the point estimates for the events that were attributable to etanercept treatment; hence, the reported events were not corrected for the different durations of exposure to etanercept or control. As the observation time is longer in the etanercept treated group, this approach is considered to be biased towards a more conservative view of safety. The statistical analysis of serious cardiovascular events was the exception to this analytical approach, and rates of these events were adjusted for exposure.

Table 3 No (%) of subjects reporting an adverse event

	Age <65 years		Age ≥65 years	
	Control* (n = 1020)	Etanercept† (n = 2652)	Control (n = 170)	Etanercept (n = 480)
Adverse event	647 (63.4)	2046 (77.1)	126 (74.1)	400 (83.3)
Serious adverse event	41 (4.0)	378 (14.3)	30 (17.6)	139 (29.0)
Infectious event	406 (39.8)	1470 (55.4)	87 (51.2)	234 (48.8)
Medically important event	13 (1.3)	105 (4.0)	12 (7.1)	50 (10.4)
Withdrawal owing to adverse event	36 (3.5)	144 (5.4)	21 (12.4)	60 (12.5)

*Subjects in control groups received either placebo or methotrexate; †subjects in the etanercept groups may have previously been included in control groups, and entered the etanercept group at a later stage of the same trial or a different trial. Data represent events occurring during etanercept treatment.

RESULTS

Subjects

A total of 3893 unique subjects with RA, JRA, PsA, and AS were included in this safety analysis: 3296 subjects aged <65 and 597 subjects ≥65 years of age (table 1). A greater proportion of subjects aged ≥65 years took part in the RA trials (17.3%) than in the PsA (5.3%) and AS (1.4%) trials. Subjects in the RA trials were predominantly female (76.3% of all subjects) and the proportion of women was similar in both age cohorts. In contrast, women represented 47.5% of all subjects in the PsA trials, yet 71.4% of patients ≥65 were female. In the AS trials, women comprised 24.2% of all patients, and all the elderly subjects were men. Subjects in all of the trials were predominantly white. Data from these trials represent 6798 subject-years of exposure to etanercept in the setting of rheumatic diseases (table 2).

Adverse events

Table 3 presents a summary of AE reported in all 22 trials. The proportion of subjects reporting AE and SAE was apparently higher in subjects aged ≥65, whether they were treated with etanercept or not (table 3). However, as shown in fig 1, when the data were normalised by subtracting background AE and SAE (the rate observed in the control group, whether receiving placebo or methotrexate (MTX)), there were no significant differences based on the observed CI of AE or SAE between the two age groups. A higher proportion of elderly subjects than subjects under 65 years of age withdrew from the studies owing to an AE, regardless of treatment group (table 3).

Infectious events

The proportion of subjects reporting an IE was higher in younger subjects receiving etanercept than in elderly subjects (table 3), which was primarily related to the higher rates of upper respiratory track infections in younger subjects. In contrast, a higher percentage of elderly subjects reported an MII compared with younger subjects. Figure 2 shows that when the data were normalised by subtracting the event rates of subjects in the control groups, overlapping CI indicated that there was no significant difference between subjects aged <65 and those aged ≥65 in reporting an MII. No cases of tuberculosis were seen in either age group.

Cardiovascular diseases

Rates of cardiovascular events were no higher in elderly subjects than in younger subjects when adjusted for the longer duration of exposure to etanercept (table 4) and after the data were normalised by subtracting the background cardiovascular events (fig 3). A total of 57/650 (8.8%) subjects aged ≥65 reported a serious cardiovascular event; 50 of these subjects received at least one dose of etanercept and seven subjects received either placebo or MTX. In contrast, 83/3672 (2.3%) of subjects aged <65 reported a cardiovascular event: 78 subjects received etanercept and five received either placebo or MTX.

Demyelinating disorders

In the pooled safety analysis of rheumatic diseases reported here, eight cases of demyelinating disorders were seen in subjects aged <65, which included six subjects in the RA

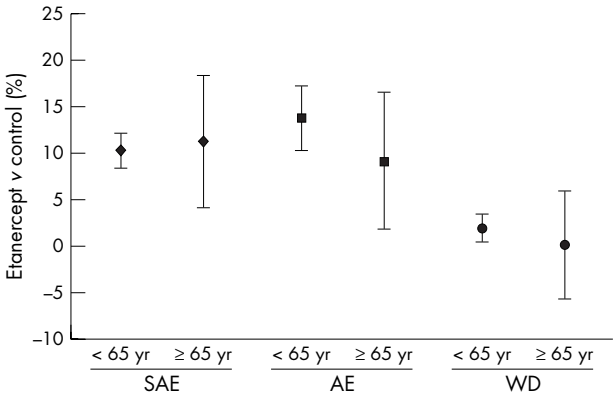

Figure 1 AE and subject withdrawals owing to AE are not significantly higher in elderly subjects. Data points represent the difference in the proportion of subjects in treatment and control groups (percentage of subjects in etanercept treatment group – percentage of subjects in control groups) reporting AE, SAE, and subject withdrawals owing to AE (WD). Error bars represent 95% CIs.

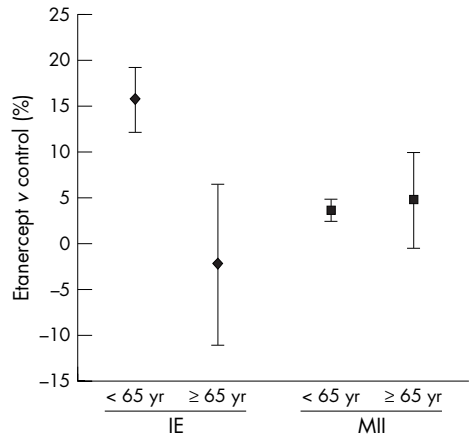

Figure 2 IE are higher in subjects aged <65. Data points represent the difference in the proportion of subjects in the treatment and control groups (percentage of subjects in etanercept treatment group – percentage of subjects in control groups) reporting IE and MII. Error bars represent 95% CIs.

Table 4 Exposure adjusted rates of cardiovascular events

	Age <65 years		Age ≥65 years	
	Control*	Etanercept	Control*	Etanercept
Number of events	10	110	11	74
Exposure (subject-years)	699	5895	75	903
Exposure adjusted rate†	1.43	1.87	14.67	8.19
SIR (95% CI)	1.30 (0.08 to 4.48)		0.56 (0.24 to 1.07)	

SIR, standardised incidence ratio; CI, confidence interval.
*Subjects in control groups received either placebo or methotrexate;
†exposure adjusted rate = number of events per subject-year.

trials and two subjects with PsA. No cases of demyelinating disease in subjects aged ≥65 were reported (fig 3).

Malignancies

Malignancy standardised incidence ratios (SIR), adjusted for age and sex, were similar for subjects aged <65 and elderly patients who had received at least one dose of etanercept (fig 4). Figure 5 shows that the incidence of overall malignancies (including lymphoma) remained stable over time and was comparable with, or less than, that expected in the RA population as the duration of exposure to etanercept increased.

Deaths

A total of 41 deaths were reported in the integrated database: 21 in subjects under the age of 65, and 20 in subjects ≥65 years of age (table 5). Half of the deaths in the elderly subjects (10/20) were due to cardiac events, whereas gastrointestinal disorders and neoplasms were the most common cause of death in the younger subjects. The number of expected deaths, based on the number of subject-years of exposure to etanercept, was 29 and 30 for subjects aged ≥65 and subjects aged <65, respectively (table 6).

DISCUSSION

The subjects included in this analysis represent several rheumatic diseases: RA, PsA, and AS. Elderly subjects who were aged ≥65 were a minority population in all studies, particularly in the PsA and AS trials. Nevertheless, the integrated dataset reported here represented considerable duration of exposure to etanercept in elderly subjects. The multistudy database of safety events from these trials also included 357 subjects with JRA, with 370 subject-years of exposure to etanercept. These young subjects comprised 11% of the subjects under the age of 65 described here, representing a minority of the subjects in the analysis. It is likely that the inclusion of these subjects improved the safety profile of the group of subjects under the age of 65, and would have accentuated differences between the two age groups. Similarly, the inclusion of subjects from the AS and PsA trials, who were predominately younger, would also have accentuated the differences between the two age groups.

Differences in AE and SAE between treatment and control groups were consistent across age cohorts; however, IE were raised in the younger subjects receiving etanercept relative to subjects receiving placebo or MTX. This difference was due primarily to an increased incidence of upper respiratory infections[14] in younger subjects receiving etanercept. This result is consistent with safety data in trials of etanercept in subjects with psoriasis. In the pooled analysis described here, a higher percentage of elderly subjects than younger subjects reported an MII. Although not significantly different from the results for the age matched control group, these data are

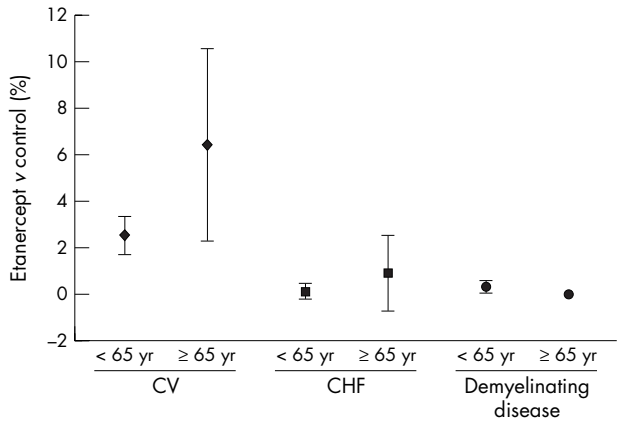

Figure 3 Cardiovascular disease, congestive heart failure, and demyelinating disorders were not increased in elderly subjects. Data points represent the difference in the proportion of subjects in treatment and control groups (percentage of subjects in etanercept treatment group – percentage of subjects in control groups) reporting cardiovascular (CV) events, CHF, and demyelinating disease. Error bars represent 95% CIs.

clinically significant, and suggest that the severity of IE may be greater in subjects aged ≥65.

Biological treatments that target TNF have been associated with the reactivation of tuberculosis (and other opportunistic infections), increased mortality of subjects with CHF, and the development and exacerbation of demyelinating diseases, and lymphomas.[14 31–33]

The association between etanercept and reactivation of tuberculosis is weaker than that seen with other TNF antagonists, and the reason for this discrepancy is unclear. Possible explanations may be the shorter half life of etanercept, the lower peak serum concentration after subcutaneous administration, or the area under the etanercept serum concentration-time curve between administrations. It has been suggested that more sustained neutralisation of TNF with the monoclonal antibodies infliximab or adalimumab may place the patient at higher risk for opportunistic infections such as tuberculosis.[34] No cases of tuberculosis were seen in the etanercept trials reported here.

Recent studies have shown that patients with RA have a higher rate of cardiovascular disease, which can remain silent,[35 36] and a higher likelihood of developing CHF.[37] The reasons for these observations may well be related to the

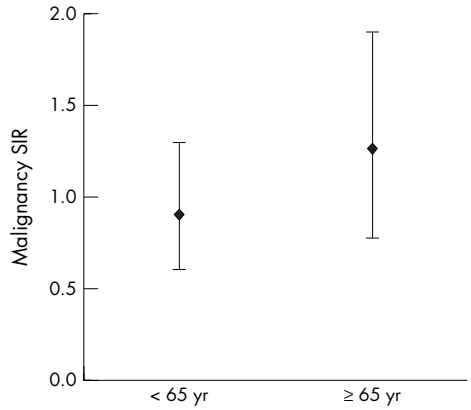

Figure 4 Malignancy rates are similar in young and elderly subjects. Data points represent malignancy standardised incidence ratios (SIR) adjusted for age and sex in subjects receiving at least one dose of etanercept. Error bars represent 95% CIs.

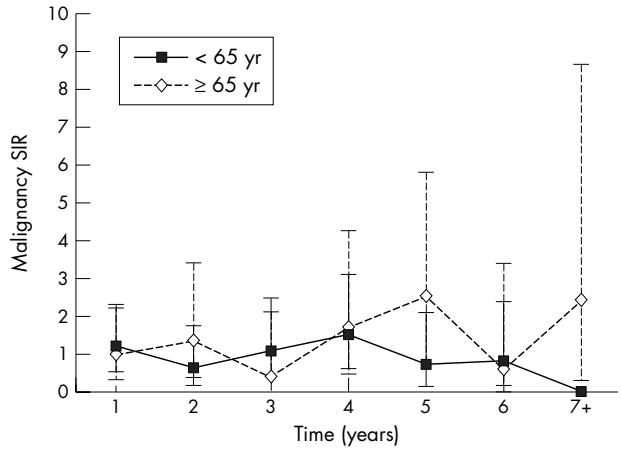

Figure 5 Malignancy rates are stable over time. Data points represent age and sex adjusted malignancy standardised incidence ratios (SIR) for subjects aged <65 and ⩾ 65. Error bars represent 95% CIs for younger (solid error bars) and elderly (dashed error bars) subjects.

Table 5 Numbers and causes of death

Causes of death	Age <65 Years (n = 3296)	Age ⩾65 Years (n = 597)
Cardiac disorders	2	10
Gastrointestinal disorders	4	1
General disorders	1	1
Hepatobiliary disorders	1	0
Infections and infestations	1	4
Injury	1	0
Neoplasms (benign, malignant, unspecified)	4	1
Nervous system disorders	3	0
Respiratory (thoracic and mediastinal disorders)	3	2
Vascular disorders	1	1
Total deaths	21	20

chronic inflammation associated with RA.[35] Patients with PsA also appear to be at increased risk of cardiovascular disease associated with inflammation.[38 39] Recent reports of heart failure in patients receiving TNF modulating treatments[40 41] must therefore be interpreted in the context of the increased risk of heart disease in this patient population. There have also been reports[42] that indicated that there was no exacerbation of CHF or increased mortality in patients treated with anti-TNF agents. As cardiovascular disease also increases with age, our statistical approach of normalising the data by subtracting the rate of cardiovascular events in control subjects from the rates seen in elderly subjects receiving etanercept and adjusting for exposure was used to determine whether these events were associated with the use of the study drug in elderly subjects. The data in this multistudy analysis suggest that the use of etanercept is not associated with higher rates of serious cardiovascular events in either age cohort.

Although the causal relationship is unclear, TNF antagonists have been associated with rare cases of new onset or exacerbation of demyelinating diseases. Animal models have suggested a role for TNF in the development of inflammatory demyelinating disease.[43] A recent review suggested that the rate of new cases of multiple sclerosis in patients receiving TNF antagonists did not differ from the rate of cases in the general population.[43] A total of eight cases of demyelinating disease were noted in the studies presented here, and none was seen in subjects aged 65 years and older.

Patients with RA have not been shown to have an increased risk of malignancies,[31] with the exception of lymphomas.[44 45] The SIR of lymphomas has been estimated to be 1.9 (95% CI 1.3 to 2.7) [45] to 2.0 (95% CI 1.5 to 2.6).[44] The risk of lymphoma was lowest in patients with low inflammatory activity (odds ratio (OR) = 1.0) and increased in patients with medium (OR = 5.4; 95% CI 0.7 to 42.0) and high (OR = 25.8; 95% CI 3.1 to 213.0) [45] in a population based cohort study of 11 683 patients. In a prospective study of 18 572 patients, the SIR for lymphomas in patients treated with etanercept was 3.8 (95% CI 1.9 to 7.5).[46] Currently, there are insufficient data to link biological treatments with increased rates of lymphoma in patients with RA. Our data suggest that the use of etanercept does not increase the risk of malignancy in patients with RA, and the malignancy rates are stable over time.

RA,[47] PsA,[48] and AS[49] are associated with increased mortality. In a recent analysis of 13 studies, the most common causes of death in patients with RA and the general United States population were cardiovascular disease, cancer, and infection; however, the life span of the patients with RA was decreased by 5–15 years.[50] Based on age adjusted estimates, our results show fewer deaths than would be expected in subjects aged ⩾65.[51]

Rheumatic diseases are associated with significant comorbidities, including infections, cardiovascular disease, and lymphomas. The role of drug treatment as a contributing factor, separate from the effects of the disease itself, is a complicated construct that is not fully understood at the present time and deserves further study and analysis. The investigators recognise that the elderly subjects enrolled in these clinical trials are not truly representative of elderly patients with rheumatic disease treated in community settings. This is largely owing to fulfilment of the strict inclusion and exclusion criteria required by the clinical trials, which limits the interpretation and generalisability of this safety analysis. Nevertheless, the data summarised here, representing a large and well studied prospective clinical trial database, indicate that etanercept is well tolerated and safe in

Table 6 Expected deaths in etanercept trials for rheumatic conditions

	Age <65 years			Age ⩾65 years		
	Expected*	Observed	SIR† (95% CI)	Expected*	Observed	SIR† (95% CI)
RA	28.9	20	0.69 (0.42 to 1.07)	29.0	20	0.69 (0.42 to 1.07)
PsA	1.1	1	0.91 (0.02 to 5.07)	0.4	0	0.00 (0.00 to 9.22)
AS	0.2	0	0.00 (0.00 to 18.44)	0.0	0	N/A

SIR, standardised incidence ratio; CI, confidence interval; RA, rheumatoid arthritis; PsA, psoriatic arthritis; AS, ankylosing spondylitis; N/A, not applicable
*Expected number of deaths per National Vital Statistics Report for 1999[51]; †standardised incidence ratio for observed deaths/expected deaths.

elderly subjects with RA, PsA, and AS, and that subjects aged ⩾65 years are at no greater risk of AE than younger subjects.

ACKNOWLEDGEMENTS

We thank all of the individual physicians and their study staff, as well as the subjects of these trials, for their thoughtful participation. We thank Julia R Gage for editorial assistance and Lizhi Xie and Ellen Lin for SAS programming support.

This work was supported by Immunex Corporation, a wholly owned subsidiary of Amgen Inc, and by Wyeth.

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