EXTENDED REPORT

Safety of extended treatment with anakinra in patients with rheumatoid arthritis

R M Fleischmann, J Tesser, M H Schiff, J Schechtman, G-R Burmester, R Bennett, D Modafferi, L Zhou, D Bell, B Appleton

Ann Rheum Dis 2006;**65**:1006–1012. doi: 10.1136/ard.2005.048371

See end of article for authors' affiliations

Correspondence to: Professor Roy Fleischmann, University of Texas Southwestern Medical Center at Dallas, Radiant Research, 5939 Harry Hines Boulevard, Dallas, Texas 75235, USA; royfleischmann@radiantresearch.com

Accepted 17 December 2005
Published Online First 5 January 2006

Objective: To determine the safety profile of anakinra after extended exposure in a diverse clinical trial population of patients with rheumatoid arthritis.

Methods: A six month, randomised, double blind phase comparing anakinra (100 mg/day) with placebo was followed by open label anakinra treatment for up to three years in patients with rheumatoid arthritis. Concomitant non-steroidal anti-inflammatory drugs, corticosteroids, and other disease modifying antirheumatic drugs were permitted.

Results: In all 1346 patients with rheumatoid arthritis received anakinra for up to three years. Patients had varying levels of disease severity, concomitant drug use, and comorbid conditions. Cumulative, exposure adjusted event (EAE) rates for all adverse events (AEs), serious AEs, and deaths were similar during each year of anakinra treatment; the overall rate (0 to 3 years) was similar to that observed for controls during the blinded phase. The most frequent AEs were injection site reactions (122.26 events/100 patient-years), rheumatoid arthritis progression (67.80 events/100 patient-years), and upper respiratory infections (26.09 events/100 patient-years). The EAE rate of serious infections was higher for patients treated with anakinra for 0 to 3 years (5.37 events/100 patient-years) than for controls during the blinded phase (1.65 events/100 patient-years). However, if the patient was not receiving corticosteroid treatment at baseline, the serious infection rate was substantially lower (2.87 event/100 patient-years). The overall incidence of malignancies was consistent with expected rates reported by SEER. Neutralising antibodies developed in 25 patients, but appeared to be transient in 12; neutralising antibody status did not appear related to occurrence of malignancies or serious infections. There were no clinically significant trends in laboratory data related to anakinra.

Conclusion: Anakinra is safe and well tolerated for up to three years of continuous use in a diverse population of patients with rheumatoid arthritis.

Anakinra (recombinant methionyl human interleukin 1 (IL1) receptor antagonist (r-metHuIL1ra)), a recombinant form of the naturally occurring IL1ra, acts as a specific blocker of IL1 signalling. Preclinical studies showed reduced inflammation and joint damage in various animal models of rheumatoid arthritis.[1–3] Subsequent human trials have demonstrated the efficacy and safety of anakinra in diverse populations with active rheumatoid arthritis: as a single agent, anakinra resulted in significant improvement in symptoms[4 5] as well as inhibition of radiographic progression.[4 6] Symptomatic improvement was also observed for anakinra used in combination with methotrexate.[7]

To provide a comprehensive analysis of long term safety of anakinra, a large, international, multicentre trial was conducted in a broad variety of patients. This sample was intended to reflect the population of typical patients treated at rheumatology clinics. Data from the double blind phase of this study were reported previously and showed similar overall frequencies of adverse events and deaths for anakinra treated and placebo treated patients, except that the frequency of serious infections was somewhat higher for anakinra treated patients.[8] Post hoc analyses revealed that safety outcomes among patients with comorbid conditions who were considered at high risk for the occurrence of adverse events[9] and among those who used concomitant corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and disease modifying antirheumatic drugs (DMARDs)[10] were similar to those reported for the overall cohort. The current report describes the safety of anakinra for durations of up to three years of treatment during the open label extension phase of the study.

METHODS

Study design

The institutional review boards or ethics committees of all participating centres approved the protocol. The study comprised an initial six month, randomised, double blind phase comparing anakinra (100 mg/day) with placebo, followed by an open label phase open to all patients who completed the randomised phase. In the open label phase, patients received anakinra (100 mg/day) for up to 30 months. Thus patients originally assigned to anakinra received anakinra for up to 36 months. The study drug was administered as daily subcutaneous injections, either by the patient or by a caregiver.

Use of concomitant NSAIDs, corticosteroids, and DMARDs was permitted during the study, with the provision that the doses had been stable for one month (NSAIDs and corticosteroids) or two months (DMARDs) before randomisation. Treatment with tumour necrosis factor inhibitors was not permitted. Doses and combinations of concomitant drugs were determined by the treating physician and could be

Abbreviations: DMARD, disease modifying antirheumatic drug; EAE, exposure adjusted event; IL1, interleukin 1; IL8, interleukin 8; NSAID, non-steroidal anti-inflammatory drug; SEER, surveillance, epidemiology, and end results database (National Cancer Institute); SIR, standardised incidence ratio

Table 1 Baseline characteristics of patients in the double blind and open label study populations

Variable	Double blind (n = 1399)	Open label (n = 1103)
Demographics		
Female (n (%))	1045 (74.7)	819 (74.3)
Age (y) (mean (range))	55.2 (19 to 85)	54.8 (19 to 85)
White race (n (%))	1235 (88.3)	985 (89.3)
Disease status (mean (range))		
Time since diagnosis of RA (y)	10.3 (0.2 to 59.5)	10.2 (0.2 to 59.5)
Tender/painful joint count	22.6 (0 to 68)	22.2 (0 to 68)
Swollen joint count	18.7 (0 to 66)	18.2 (0 to 66)
C reactive protein (mg/dl)*	2.67 (<0.1 to 25.6)	2.52 (<0.1 to 25.6)
Concomitant drug treatment (n (%))†		
DMARDs	1090 (77.9)	888 (80.5)
Methotrexate	748 (53.5)	619 (56.1)
Corticosteroids	814 (58.2)	654 (59.3)
NSAIDs	1223 (87.4)	975 (88.4)

*C reactive protein values below detection limit are set at 0.09 for calculation of summary statistics.
†Numbers of patients are not additive, as many used more than one concomitant drug.
DMARD, disease modifying anti-rheumatic drug; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; y, years.

modified if clinically indicated. Dose modifications were not permitted for anakinra; in the case of an adverse event that prevented administration of a full dose, anakinra was withheld until symptoms resolved.

Study visits were conducted on day 1, week 1, months 1, 3, 6, 7, and 9, and then every three months until month 36, and at discontinuation for patients who withdrew early. Adverse events were coded by preferred term and body system according to the World Health Organisation (WHO) *Adverse Reaction Terminology* dictionary. Serious infections were defined as infections that met the definition of a serious adverse event, including hospital admissions and the use of intravenous antibiotics. Opportunistic infections were identified in accordance with guidelines of the US Centers for Disease Control (CDC).[11] Laboratory values were assessed using the WHO toxicity grading criteria.

Patients

Eligible patients were ⩾18 years of age, had been diagnosed with rheumatoid arthritis based on American College of Rheumatology 1987 diagnostic criteria three months or more before study entry, and had active disease, defined as the presence of three or more swollen joints and three or more tender/painful joints, or ⩾45 minutes of morning stiffness. Patients with the following uncontrolled medical conditions were excluded: diabetes with HbA_{1c} >8%; white blood cell (WBC) count $<2\times10^9$/l; neutrophil count $<1\times10^9$/l; platelet count $<100\times10^9$/l; aspartate transaminase or alanine transaminase ⩾1.5 times the upper limit of normal; malignancy other than basal cell carcinoma of the skin or in situ carcinoma of the cervix within the previous five years; hepatitis B or C virus or HIV. Women were excluded if they were pregnant or breast feeding or were unwilling to use adequate contraceptives. All patients provided written informed consent before any study procedures were undertaken.

Antibody assays

Serum samples were drawn at months 3, 6, 9, and 12, and then every six months until month 36, and at the final study visit for patients who withdrew early. Samples were assayed for the presence of antibodies against anakinra using an enzyme linked immunosorbent assay. Samples with a positive result were subjected to a confirmatory biosensor assay (BIAcore 3000) and then analysed for the ability to neutralise anakinra induced inhibition of IL1β induced IL8 production in COS-1 cells.

Statistical methods

This safety analysis included all patients who were randomised and received at least one dose of anakinra. The primary safety end points were rates of all adverse events, serious adverse events, deaths, and serious infections, and the percentage of patients who withdrew from the study because of an adverse event. Rates of adverse events that occurred during treatment or within 30 days of stopping anakinra were analysed as cumulative exposure adjusted event (EAE) rates (number of events/100 patient-years of exposure).

Table 2 Overall cumulative exposure adjusted event rates for adverse events

	EAE rate on exposure to anakinra* (No of events per 100 patient-years)			
Adverse event	Placebo† (E = 120.9)	0 to 1 y (E = 1041.8)	0 to 2 y (E = 1754.8)	0 to 3 y (E = 2273.0)
All AEs	1029.4	990.0	779.2	689.8
SAEs	22.3	26.5	27.7	27.1
Serious infections	1.6	5.2	5.5	5.4
Deaths	0.8	0.6	0.6	0.7

*Cumulative EAE rates in the specified period for 1116 patients randomly assigned to anakinra (873 of whom continued treatment during the open label extension) and 230 patients randomly assigned to placebo who received at least one dose of anakinra during open label.
†Cumulative exposure adjusted event rates for patients who received placebo during the randomised, double blind phase.
AE, adverse event; E, number of patient-years of exposure; EAE, exposure adjusted event; SAE, serious adverse event; y, years.

Table 3 Cumulative exposure adjusted event rates for the most frequent adverse events*

Adverse event	EAE rate on exposure to anakinra† (No of events per 100 patient-years) Placebo‡ (E = 120.9)	0 to 1 y (E = 1041.8)	0 to 2 y (E = 1754.8)	0 to 3 y (E = 2273.0)
Injection site reactions	135.60	260.12	157.80	122.26
RA progression	122.37	77.46	72.43	67.80
URTI	58.70	33.88	27.81	26.09
Headache	32.25	35.52	23.31	19.05
Arthralgia	19.02	16.41	15.44	13.77
Sinusitis	18.19	15.65	13.16	12.80
Nausea	19.02	20.25	(14.82	12.45
Diarrhoea	16.54	17.09	12.88	11.26

*Adverse events occurring at rates of ⩾10 events per 100 patient-years.
†Cumulative exposure adjusted event rates in the specified period for 1116 patients randomly assigned to anakinra (873 of whom continued treatment during the open label extension) and 230 patients randomly assigned to placebo who received at least one dose of anakinra the during open label extension.
‡Cumulative exposure adjusted event rates for patients who received placebo during the randomised, double blind phase.
E, number of patient-years of exposure; EAE, exposure adjusted event; RA, rheumatoid arthritis; URTI, upper respiratory tract infection, y, years.

The incidence of malignancies (excluding basal and squamous cell carcinomas of the skin and all in situ malignancies other than those of the urinary bladder, which are included with other urinary system cancers) among patients treated with anakinra was compared with that of the general population, using data from the National Cancer Institute surveillance, epidemiology, and end results (SEER) database.[11] Standardised incidence ratios were adjusted for age, sex, and race.

RESULTS

Patient characteristics and exposure to anakinra

In all, 1346 patients (1116 randomly assigned to anakinra and 230 randomly assigned to placebo) received at least one dose of anakinra and are included in the current analysis.

Most patients in the open label cohort were white (89.3%) and female (74.3%). At study entry, the majority of patients were using NSAIDs (88.4%), corticosteroids (59.3%), or methotrexate, either alone or in combination with other drugs (56.1%). Slightly less than half were using DMARDs other than methotrexate (49.0%). These characteristics were similar to those observed in the entire randomised cohort (table 1).

Including double blind treatment, 1346 patients completed ⩽1 year of treatment with anakinra, 835 completed >1 year and ⩽2 years of treatment, 627 completed >2 and <3 years of treatment, and 510 completed 3 years of treatment. The estimated total exposure to anakinra was 1041.8 patient-years after 12 months, 1754.8 patient-years after 24 months, and 2273.0 patient-years after 36 months. Patient compliance to the daily injection schedule was excellent: the average frequencies of missed injections were 4.63%, 5.13%, and 5.33% for years 0–1, 0–2, and 0–3, respectively.

Adverse events

In all, 15 680 adverse events were reported by 1295 of the anakinra treated patients (96%), including 616 serious adverse events in 370 patients (27%), of which 122 were serious infections in 105 patients (8%). As shown in table 2, cumulative EAE rates for serious adverse events and deaths among anakinra treated patients were similar during years 0–1, 0–2, and 0–3; these rates also were similar to those observed for placebo treated patients during the double blind phase of the study. The cumulative rate of serious infections for years 0–3 was low (5.4 events/100 patient-years) and relatively constant for each year of anakinra treatment. The average risk for overall adverse events did not increase with longer durations of anakinra exposure.

Over the entire period of anakinra treatment, 389 patients (28.9%) discontinued treatment because of adverse events, including disease progression, or death. The cumulative rates for withdrawal for adverse events—including events of disease progression—decreased over time (events/100 patient-years were 47.23 for years 0–1, 33.28 for years 0–2, and 28.07 for years 0–3); by the second year of treatment, they were comparable to the rate observed for placebo subjects during the six month blinded phase (33.90 events/100 patient-years). The most common event leading to

Table 4 Cumulative exposure adjusted event rates for the most frequent serious adverse events and serious infections*

Adverse event	EAE rate on exposure to anakinra† (No of events per 100 patient-years) Placebo‡ (E = 120.9)	0 to 1 y (E = 1041.8)	0 to 2 y (E = 1754.8)	0 to 3 y (E = 2273.0)
RA progression	4.96	1.73	2.74	2.90
Fractures	0.83	0.86	1.08	1.19
Pneumonia	0.00	1.25	1.25	1.28

*Most frequent serious adverse events or infections were those occurring at rates of ⩾1.0 event per 100 patient-year for the 0–3 year period.
†Cumulative exposure adjusted event rates in the specified period for 1116 patients randomly assigned to anakinra (873 of whom continued treatment during the open label extension) and 230 patients randomly assigned to placebo who received at least one dose of anakinra during the open label extension.
‡Cumulative exposure adjusted event rates for patients who received placebo during the randomised, double blind phase.
E, number of patient-years of exposure; EAE, exposure adjusted event; RA, rheumatoid arthritis; y, years.

Table 5 Cumulative exposure adjusted event rates for the most frequent serious infections (n ⩾2) by preferred term after three years of anakinra exposure (without steroid use at baseline *v* with steroid use at baseline)

Without corticosteroid use at baseline (n = 569) (E = 940.3)			With corticosteroid use at baseline (n = 777) (E = 1332.7)		
Preferred term	**n**	**EAE rate***	**Preferred term**	**n**	**EAE rate***
Any	27	2.87	Any	95	7.13
Pneumonia	9	0.96	Pneumonia	20	1.50
Cellulitis	2	0.21	Cellulitis	16	1.20
Diverticulitis	2	0.21	Infection	9	0.68
Lower respiratory infection	2	0.21	Sepsis	5	0.38
			Abscess abdomen	3	0.23
			Bronchitis	3	0.23
			Infection bacterial	3	0.23
			Osteomyelitis	3	0.23
			Pneumonia lobar	3	0.23
			Gastroenteritis	2	0.15
			Pneumonia bacterial	2	0.15
			Pyelonephritis	2	0.15
			Upper respiratory infection	2	0.15

*Number of events per 100 patient-years.
E, number of patient-years of exposure; EAE, exposure adjusted event.

withdrawal was injection site reactions (9.46 events/100 patient-years). During year 0–1, 199 patients withdrew because of injection site reactions, but only five patients withdrew for this reason during year 1–2 and none during year 2–3. Progression of rheumatoid arthritis was the second most common event leading to withdrawal (4.88 events/100 patient-years); the next three most common events leading to withdrawal (headache, cellulitis, and pneumonia) all occurred at cumulative rates of <1 event/100 patient-years.

Adverse events with the highest cumulative EAE rates during 0–3 years of anakinra exposure were injection site reactions (122.26 events/100 patient-years), rheumatoid arthritis progression (67.80 events/100 patient-years), and upper respiratory infections (26.09 events/100 patient-years) (table 3). The cumulative EAE rates of injection site reactions, rheumatoid arthritis progression, and upper respiratory tract infections decreased during each year. Headaches, arthralgia, sinusitis, nausea, and diarrhoea all occurred at rates of ⩽20 events/100 patient-years. Each of these overall event rates was lower than that observed for placebo treated patients during the double blind phase.

The most frequent serious adverse events and serious infections (EAE rates of ⩾1 event/100 patient-years) were rheumatoid arthritis progression, fractures, and pneumonia (table 4). In addition, serious infection rates of anakinra treated patients receiving corticosteroids at baseline were compared with rates of anakinra treated patients not receiving corticosteroids at baseline (table 5). Anakinra treated patients receiving concomitant corticosteroid treatment at baseline were much more likely to experience a serious infection (7.13 events/100 patient-years (with corticosteroids) *v* 2.87 events/100 patient-years (without corticosteroids)). This phenomenon was mirrored in the two most frequently observed types of infection in both classes: pneumonia (1.5 events/100 patient-years (with corticosteroids) *v* 0.96 events/100 patient-years (without corticosteroids)) and cellulitis (1.2 events/100 patient-years (with corticosteroids) *v* 0.21 events/100 patient-years (without corticosteroids)). The rate for serious cases of rheumatoid arthritis progression increased during each successive year of treatment, but all were lower than that observed for placebo treated patients during the double blind period. Rates for serious fractures, serious cases of pneumonia, and serious cases of cellulitis were relatively constant.

Other clinically important infections

Episodes of sepsis (a common terminology criterion of ⩾grade 3) were infrequent, although cumulative EAE rates showed progressive increases with continued anakinra exposure: rates for serious episodes of sepsis were 0.10, 0.28, and 0.35 events/100 patient-years for the 0 to 1 year, 0 to 2 year, and 0 to 3 year intervals of the study. Three patients died because of sepsis.

Three distinct events meeting the CDC definition of opportunistic infections were observed in three female patients, all over 55 years of age. One event, diagnosed as an atypical mycobacterial infection, occurred approximately 19 months after initiation of anakinra treatment in a patient who had a history of reflex sympathetic dystrophy and was receiving concomitant prednisone and methotrexate. The second event, histoplasmosis, occurred approximately five months after initiation of anakinra treatment in a patient who had a history of cholecystectomy, appendectomy, and occasional indigestion. The third event, candida oesophagitis, occurred approximately 2.5 years after initiation of anakinra treatment in a patient with a history of gastro-oesophageal reflux and cirrhosis who was receiving concomitant prednisone.

Deaths

Fifteen deaths occurred during the 0 to 3 year period of treatment with anakinra or within 30 days of study completion. Causes of death included cardiac arrest/myocardial infarction (4), cerebrovascular accident (1), ventricular fibrillation (1), sepsis (3), upper gastrointestinal haemorrhage (1), metastatic malignant melanoma (1), malignant lymphoma (1), pulmonary fibrosis (2), and suicide (1). One patient with pulmonary fibrosis had a history of interstitial lung disease. Eleven of the other 14 patients who died also had relevant pre-existing medical conditions.

Malignancies

The cumulative EAE rate for all malignancies in patients treated with anakinra for up to three years was 1.2 events per 100 patient-years. The most common malignancies reported in patients treated with anakinra were squamous cell or squamous cell in situ skin carcinoma (nine events in seven patients), malignant melanoma (four events in four patients), breast carcinoma (three events in three patients), and malignant lymphoma (three events in three patients).

Table 6 Standardised incidence ratios for cancers occurring in patients treated with anakinra

Site of malignancy	Observed	Expected*	SIR	95% CI
All sites†	17	20.58	0.83	0.48 to 1.32
Oral cavity and pharynx	1	0.44	2.26	0.06 to 13.00
Digestive system	2	3.49	0.57	0.07 to 2.07
Respiratory system	1	3.19	0.31	0.01 to 1.75
Malignant melanoma	4	0.73	5.48	1.49 to 14.00
Breast	3	4.70	0.64	0.13 to1.86
Female genital system	1	1.85	0.54	0.01 to 3.02
Urinary system	2	1.23	1.63	0.20 to 5.89
Lymphoma	3	0.81	3.71	0.77 to 11.00
Other‡	0	4.13	0.00	0.00 to 0.89

*Expected numbers of cases estimated using 1992–2000 SEER database adjusted for the age, sex, and race of cohort receiving anakinra.
†Excludes malignancies that are not included in the SEER database (basal and squamous cell carcinomas of the skin and all in situ malignancies other than those of the bladder).
‡Combines all other SEER major organ system categories.
CI, confidence interval; SIR, standardised incidence ratio, calculated as observed/expected.

Analysis of malignancy data (excluding basal cell carcinoma, squamous cell carcinoma of the skin, and all in situ malignancies except those of the urinary bladder, which are included with other urinary system cancers) revealed a lower than expected overall incidence of cancer for this study population compared with data for the general population (table 6). Standardised incidence ratios (SIR) indicated a higher than expected incidence for melanoma (SIR = 5.48 (95% confidence interval (CI), 1.49 to14.00)) and lymphoma (SIR = 3.71 (0.77 to 11.0)) in patients exposed to anakinra compared with the general population. Because of the presence of additional risk factors and reporting confounders in patients with rheumatoid arthritis, it cannot yet be determined if such malignancies are related to anakinra treatment.

Antibodies to anakinra

Of 1340 anakinra treated patients tested for antibodies to anakinra, 672 (50.1%) had a positive immunoassay result at one or more time points and 25 (1.9%) were found to have neutralising antibodies. Twelve patients reverted to seronegative status for neutralising antibodies during the course of the study, and two seroconverted from positive to negative to positive. Of the 25 patients who tested positive for neutralising antibodies, 13 (52%) reported disease progression as an adverse event; in six patients, the event occurred within three months of seropositivity. No relations were seen between neutralising antibody status and occurrence of malignancies, opportunistic infections, or serious infections.

Laboratory data

No clinically significant trends were evident for haematology or clinical chemistry indices. Most patients had normal laboratory values at study entry. During the study, a few anakinra treated patients experienced grade 3 or 4 toxicities in laboratory values. Four patients experienced grade 3 or 4 decreases in haemoglobin (two had shown grade 1 decreases at study entry), and two experienced a decreased haematocrit. Five patients had increased liver enzymes, and seven had grade 3 or higher neutropenia at one or more time points. Two of these seven subjects experienced serious infectious events; in one case, the neutropenia was not associated temporally with the infectious event; in the other case, the temporal relation could not be determined. In most cases, these grade 3 or 4 toxic events were sporadic and were not associated with progressive decreases nor were indicative of drug related impairment.

DISCUSSION

Anakinra has been approved for the treatment of rheumatoid arthritis in adults, based on previously described efficacy and safety studies.[4–7] The current report confirms and extends previous safety findings by assessing prolonged treatment in a large and diverse population of adults with rheumatoid arthritis. Notably, this study included patients with varying levels of disease severity and a wide range of comorbid conditions, and allowed multimodal concomitant antirheumatic treatment; most clinical studies in rheumatoid arthritis restrict entry to patients lacking comorbid conditions and prohibit concomitant antirheumatic treatment other than methotrexate.[10 12–18] Moreover, this design allowed for greater ability to detect the occurrence of adverse events that might, in shorter term studies, occur at rates too low to be estimated accurately. Thus the results from this study should be a close approximation of those expected in the general population of patients with rheumatoid arthritis.

The cohort for this long term safety assessment comprised 1346 patients who received up to 36 months of continuous anakinra treatment. At study entry, more than 80% of patients were using NSAIDs and more than half were using corticosteroids or methotrexate, while almost 70% of patients had comorbid conditions.[9] Overall exposure to anakinra was considerable, with 510 patients completing three years of treatment. The most common adverse events leading to withdrawal were injection site reactions and rheumatoid arthritis progression, consistent with previous studies of anakinra.[4 5 7] The cumulative rates for all adverse events leading to withdrawal decreased over time, and by the second year of treatment were comparable to the rate observed for placebo subjects during the six month blinded phase (33.28 *v* 33.90 events/100 patient-years). Cumulative EAE rates for all adverse events, serious adverse events, and deaths among anakinra treated patients were similar during each of the three years of the study and also were similar to those observed for placebo treated patients during the randomised double blind phase of the study.

Patients with rheumatoid arthritis have an increased risk of infections, particularly those involving bones, joints, skin, soft tissues, and the respiratory tract, either because of underlying mechanisms of the disease itself, or because of treatment induced decreases in immune function, or both.[19–21] In the current analysis, the overall cumulative EAE rate of serious infections during extended anakinra treatment was low (5.37 events/100 patient-years), but notably was approximately threefold higher than that observed for placebo treated patients (1.6 events/100 patient-years). However, concomitant steroid use at baseline appears to

substantially increase the likelihood that an anakinra treated patient will develop an infection. These findings support the safety of anakinra over extended exposure, but also suggest that patients at high risk for infections should be carefully monitored, particularly if corticosteroid treatment is concomitant. Current labelling for anakinra contraindicates its use in patients with active infections.

The reason for increased risk of serious infections in patients with rheumatoid arthritis treated with anakinra has not been determined definitively, but may reflect immune suppression resulting from inhibition of IL1.[22] Several recent studies have found increased risk of serious infections in patients with rheumatoid arthritis treated with biological agents compared with those treated with placebo or methotrexate alone.[12 14 18] Other studies, however, have found no difference in frequencies of serious infections for such patient groups.[15–17 23–26] The reasons for these disparate findings are unclear. Corticosteroid use also has been associated with an increased risk of infections,[27–29] and a post hoc analysis of concomitant drug treatment in the six month double blind phase of the current study showed that the frequency of infections in the subset of patients who received anakinra and concomitant corticosteroids was similar to that of the overall cohort of anakinra-treated patients.[10] However, the three year safety data reported within reveal that corticosteroid use while on anakinra significantly enhances the chances of developing a serious infection.

The higher than expected incidence of melanoma observed in the current study may not be related to anakinra, as one patient had a prior history of the disease and most of the others lived in areas with high sun exposure or in close proximity to the equator. Furthermore, a higher than expected incidence of melanoma has rarely been seen in other anakinra studies.[30] Only a single case of melanoma has been observed prior to the present study, and the affected patient also had a previous history of melanoma. In clinical trials of other rheumatoid arthritis biological agents such as etanercept,[17 24 31] infliximab,[15 32 33] and adalimumab,[14 25 34–36] melanomas have not been found at rates higher than expected.

The increased risk for lymphoma is consistent with previous reports of increased risk of lymphoma in rheumatoid arthritis.[37–40] In a case–control study, patients with rheumatoid arthritis and high disease activity were estimated to have up to a 25.8-fold increased risk of lymphoma compared with controls without rheumatoid arthritis.[41] The SIR for lymphoma (3.71 (95% CI, 0.77 to 11.0)) observed in the present study is consistent with odds ratios varying from 1.9 to 20.0 in various reports of patients with rheumatoid arthritis.[37 38 42–44] Wolfe and Michaud[44] recently reported an SIR of 2.9 (95% CI, 1.7 to 4.9) for lymphoma in patients who received biological therapies. Thus the incidence ratios for patients treated with anakinra and other biological agents appear to be within the ranges observed in rheumatoid arthritis in general, and indeed, Wolfe and Michaud concluded that the existence of a causal relation between lymphoma development and use of biological therapy in patients with rheumatoid arthritis could not be determined with the available data.[44] While the current observations suggest that anakinra treatment may not be an additional risk factor for the development of lymphoma in patients with rheumatoid arthritis, continued surveillance of anakinra and other biological agents used for the treatment of this disease is warranted.

Taken together, the data presented here support the safety of extended treatment with anakinra in patients with rheumatoid arthritis. Overall, anakinra was well tolerated. Because most patients in this study used concomitant drug treatment and many had comorbid conditions, the results should be predictive of effects that would be seen in the general population of patients typically cared for in a rheumatology clinic.

ACKNOWLEDGEMENTS

We wish to thank the clinical investigators and coordinators who participated in the study, and Martha Sensel PhD for assisting with preparation of the manuscript.

The research was funded by Amgen Inc. Amgen was involved in the study design and the collection of data. Together with the authors, Amgen was involved with the analysis and interpretation of data, the writing of the report, and the decision to submit the paper for publication.

Authors' affiliations

R M Fleischmann, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, USA
J Tesser, R Bennett, Arizona Arthritis & Rheumatology Associates, Phoenix, Arizona, USA
M H Schiff, Denver Arthritis Clinic, Denver, Colorado, USA
J Schechtman, Sun Valley Arthritis Center, Glendale, Arizona, USA
G-R Burmester, Universitatsklinikum Carite, Humbolt-Universität, Berlin, Germany
D Modafferi, L Zhou, D Bell, B Appleton, Amgen Inc, Thousand Oaks, California, USA

REFERENCES

1 **Bakker AC**, Joosten LA, Arntz OJ, Helsen MM, Bendele AM, van de Loo FA, *et al*. Prevention of murine collagen-induced arthritis in the knee and ipsilateral paw by local expression of human interleukin-1 receptor antagonist protein in the knee. *Arthritis Rheum* 1997;**40**:893–900.
2 **Otani K**, Nita I, Macaulay W, Georgescu HI, Robbins PD, Evans CH. Suppression of antigen-induced arthritis in rabbits by ex vivo gene therapy. *J Immunol* 1996;**156**:3558–62.
3 **Joosten LA**, Helsen MM, van de Loo FA, van den Berg WB. Anticytokine treatment of established type II collagen-induced arthritis in DBA/1 mice. A comparative study using anti-TNF alpha, anti-IL-1 alpha/beta, and IL-1Ra. *Arthritis Rheum* 1996;**39**:797–809.
4 **Bresnihan B**, Alvaro-Gracia JM, Cobby M, Doherty M, Domljan Z, Emery P, *et al*. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum* 1998;**41**:2196–204.
5 **Nuki G**, Bresnihan B, Bear MB, McCabe D. Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002;**46**:2838–46.
6 **Jiang Y**, Genant HK, Watt I, Cobby M, Bresnihan B, Aitchison R, *et al*. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. *Arthritis Rheum* 2000;**43**:1001–9.
7 **Cohen S**, Hurd E, Cush J, Schiff M, Weinblatt ME, Moreland LW, *et al*. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002;**46**:614–24.
8 **Fleischmann RM**, Schechtman J, Bennett R, Handel ML, Burmester GR, Tesser J, *et al*. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: a large, international, multicenter, placebo-controlled trial. *Arthritis Rheum* 2003;**48**:927–34.
9 **Schiff MH**, DiVittorio G, Tesser J, Fleischmann R, Schechtman J, Hartman S, *et al*. The safety of anakinra in high-risk patients with active rheumatoid arthritis: six-month observations of patients with comorbid conditions. *Arthritis Rheum* 2004;**50**:1752–60.
10 **Tesser J**, Fleischmann R, Dore R, Bennett R, Solinger A, Joh T, *et al*. Concomitant medication use in a large, international, multicenter, placebo controlled trial of anakinra, a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis. *J Rheumatol* 2004;**31**:649–54.
11 **CDC**. Prevalence of self-reported arthritis or chronic joint symptoms among adults – United States, 2001. *MMWR Morb Mortal Wkly Rep* 2002;**51**:948–50.
12 **Edwards JC**, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, *et al*. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;**350**:2572–81.
13 **Genovese MC**, Cohen S, Moreland L, Lium D, Robbins S, Newmark R, *et al*. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 2004;**50**:1412–19.
14 **Keystone EC**, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, *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.
15 **Lipsky PE**, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, *et al*. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000;**343**:1594–602.
16 **Moreland LW**, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL, *et al*. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *N Engl J Med* 1997;**337**:141–7.
17 **Moreland LW**, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, *et al*. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med* 1999;**130**:478–86.
18 **St Clair EW**, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, *et al*. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004;**50**:3432–43.
19 **Cush JJ**. Safety overview of new disease-modifying antirheumatic drugs. *Rheum Dis Clin North Am* 2004;**30**:237–55.
20 **Doran MF**, Gabriel SE. Infections in rheumatoid arthritis – a new phenomenon? *J Rheumatol* 2001;**28**:1942–3.
21 **Doran MF**, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum* 2002;**46**:2287–93.
22 **Segal BH**, Sneller MC. Infectious complications of immunosuppressive therapy in patients with rheumatic diseases. *Rheum Dis Clin North Am* 1997;**23**:219–37.
23 **Genovese MC**, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, *et al*. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002;**46**:1443–50.
24 **Bathon JM**, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, *et al*. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;**343**:1586–93.
25 **Furst DE**, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, *et al*. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol* 2003;**30**:2563–71.
26 **Moreland LW**, Cohen SB, Baumgartner SW, Tindall EA, Bulpitt K, Martin R, *et al*. Long-term safety and efficacy of etanercept in patients with rheumatoid arthritis. *J Rheumatol* 2001;**28**:1238–44.
27 **Doran MF**, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. *Arthritis Rheum* 2002;**46**:2294–300.
28 **Saag KG**, Koehnke R, Caldwell JR, Brasington R, Burmeister LF, Zimmerman B, *et al*. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. *Am J Med* 1994;**96**:115–23.
29 **van Albada-Kuipers GA**, Linthorst J, Peeters EA, Breedveld FC, Dijkmans BA, Hermans J, *et al*. Frequency of infection among patients with rheumatoid arthritis versus patients with osteoarthritis or soft tissue rheumatism. *Arthritis Rheum* 1988;**31**:667–71.
30 Kineret (anakinra) FDA briefing information, 16 August 2001. http://www.fda.gov/ohrms/dockets/ac/01/briefing/3779b1_01_Amgen.pdf (accessed 18 November 2005).
31 **Weinblatt ME**, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, *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.
32 **Maini RN**, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, *et al*. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;**41**:1552–63.
33 **Maini R**, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, *et al*. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999;**354**:1932–9.
34 **Weinblatt ME**, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, *et al*. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003;**48**:35–45.
35 **van de Putte LB**, Rau R, Breedveld FC, Kalden JR, Malaise MG, van Riel PL, *et al*. Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. *Ann Rheum Dis* 2003;**62**:1168–77.
36 **van de Putte LB**, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, *et al*. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* 2004;**63**:508–16.
37 **Gridley G**, McLaughlin JK, Ekbom A, Klareskog L, Adami HO, Hacker DG, *et al*. Incidence of cancer among patients with rheumatoid arthritis. *J Natl Cancer Inst* 1993;**85**:307–11.
38 **Prior P**, Symmons DP, Hawkins CF, Scott DL, Brown R, *et al*. Cancer morbidity in rheumatoid arthritis. *Ann Rheum Dis* 1984;**43**:128–31.
39 **Symmons DP**, Ahern M, Bacon PA, Hawkins CF, Amlot PL, Jones EL, *et al*. Lymphoproliferative malignancy in rheumatoid arthritis: a study of 20 cases. *Ann Rheum Dis* 1984;**43**:132–5.
40 **Symmons DP**. Neoplasms of the immune system in rheumatoid arthritis. *Am J Med* 1985;**78**:22–8.
41 **Baecklund E**, Ekbom A, Sparen P, Feltelius N, Klareskog L, *et al*. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. *BMJ* 1998;**317**:180–1.
42 **Isomaki HA**, Hakulinen T, Joutsenlahti U. Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. *J Chronic Dis* 1978;**31**:691–6.
43 **Tennis P**, Andrews E, Bombardier C, Wang Y, Strand L, West R, *et al*. Record linkage to conduct an epidemiologic study on the association of rheumatoid arthritis and lymphoma in the Province of Saskatchewan, Canada. *J Clin Epidemiol* 1993;**46**:685–95.
44 **Wolfe F**, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis Rheum* 2004;**50**:1740–51.