Effects of Anakinra Monotherapy on Joint Damage in Patients with Rheumatoid Arthritis. Extension of a 24-Week Randomized, Placebo-Controlled Trial

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ABSTRACT. ***Objective.*** To determine the effects of treatment on the radiologic manifestations of joint damage in patients with rheumatoid arthritis (RA) who participated in a 24-week extension study of a randomized, placebo-controlled clinical trial of anakinra, a recombinant human interleukin 1 receptor antagonist.

Methods. The patients had entered a 24-week, randomized, double-blind, placebo-controlled study. Anakinra was self-administered by subcutaneous injection of 30, 75, or 150 mg/day. Upon completion of the placebo-controlled phase, the patients entering the extension study who had received placebo were randomized to one of the 3 treatment dosages for a further 24 weeks, and the patients who had been initially randomized to one of the 3 anakinra dosages continued to receive the same dosage. Radiographs of the hands were obtained at baseline and at 24 and 48 weeks. The radiographs were evaluated using a modified Sharp method.

Results. A total of 472 patients were recruited. The mean change in the total modified Sharp score of 178 patients who completed 48 weeks treatment, including all dosages, was significantly less than the change observed in 58 patients who received placebo for 24 weeks and anakinra for 24 weeks ($p = 0.015$). A significant reduction in the change of the total modified Sharp score was observed in the patients who received anakinra 75 and 150 mg/day. The total modified Sharp score was reduced significantly more during the second 24-week treatment period, compared to the first ($p < 0.001$). Significant reductions in the second 24-week period were observed following anakinra 75 mg/day ($p = 0.006$) and 150 mg/day ($p = 0.008$).

Conclusion. Patients with RA who received anakinra for 48 weeks demonstrated significant slowing of radiographic joint damage. The treatment effect observed after the first 24-week period appeared to increase when anakinra was continued for 48 weeks. (J Rheumatol 2004;31:1103–11)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
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Rheumatoid arthritis (RA) is characterized by chronic inflammation of the synovial membrane, which can extend as a pannus over adjacent articular cartilage[1]. Many activated cell populations participate in complex pathophysiologic pathways that result in progressive degradation of cartilage and bone. The resulting joint damage is associated with increasing loss of function[2].

Interleukin 1 receptor antagonist (IL-1Ra), like IL-1α and IL-1ß, is produced primarily by activated monocytes and tissue macrophages[3]. The agonistic effects of IL-1α and IL-1ß are partially blocked by the interaction between IL-1Ra and the type I IL-1 receptor (IL-1RI)[4,5]. When IL-1Ra binds to IL-1RI, it blocks the binding of IL-1α and IL-1ß and inhibits signal transduction. The role of IL-1Ra in downregulating IL-1-mediated pathophysiologic pathways was demonstrated in IL-1Ra knockout mice that developed a form of chronic arthritis closely resembling human RA[6]. IL-1ß, tumor necrosis factor-α (TNF-α), and IL-6 were overexpressed in the joint tissues, highlighting the importance of IL-1Ra in regulating local proinflammatory and tissue-damaging cytokine networks.

The effects of recombinant human IL-1Ra (anakinra) treatment on the signs and symptoms of RA were observed in randomized, placebo-controlled clinical trials of 24 weeks[7,8]. Treatment with anakinra modulated the immunohistologic appearances of synovial inflammation[9]. Anakinra was also shown to reduce the rate of progressive joint damage over 24 weeks, as measured by both the Larsen and the Genant modification of the Sharp scoring methods[7,10]. We evaluated the protective effects of anakinra on progressive joint damage in a 24-week extension of the original 24-

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week placebo-controlled monotherapy study[7]. Patients who received anakinra treatment for the entire 48 weeks had significantly less joint damage than patients who received placebo for 24 weeks before starting anakinra. Moreover, patients who received anakinra for 48 weeks showed greater retardation of joint damage during the second 24 weeks, suggesting that the protective effects of anakinra treatment on joint damage may increase over time.

MATERIALS AND METHODS

Patients. The eligibility criteria and the design of the study have been described[7]. In brief, patients were eligible for the study if they had active RA, were aged between 18 and 75 years, and had symptoms for more than 6 months and less than 8 years. Active disease was defined as the presence of 10 or more swollen joints and at least 3 of the following 4 criteria: 10 or more tender or painful joints, disease activity graded as severe or very severe by the physician, and a C-reactive protein (CRP) concentration > 1.5 mg/dl. Doses of nonsteroidal antiinflammatory drugs and corticosteroids (≤ 10 mg/day) remained constant for the duration of the study. Disease-modifying antirheumatic drugs (DMARD) were discontinued at least 6 weeks prior to enrollment. Patients that had previously received other biologic agents were not eligible for the study.

Study protocol. Patients were randomized into one of 4 treatment groups: placebo or anakinra 30 mg, 75 mg, or 150 mg/day by a single, self-administered subcutaneous injection (Figure 1). Patients and assessors were blinded to the treatment administered. Upon completion of the 24-week placebo-controlled phase, all patients were invited to enter a 24-week extension study[11]. Patients who had received placebo for the initial 24 weeks were randomized to one of the 3 anakinra treatment groups; patients who had received anakinra treatment continued to receive the same dosage. Patients and assessors remained blinded to the treatment administered, during both the initial placebo-controlled and extension phases. The primary efficacy endpoint was the American College of Rheumatology (ACR) composite score[12]. Nine secondary clinical efficacy endpoints were also selected as described[7].

Radiographs of the hands and wrists with posteroanterior projection obtained at Weeks 0, 24, and 48 were scored according to Genant's modification of Sharp's method[10]. Radiographs were scored in pairs or triplicates and in random sequence order by one author (HKG). Erosions, including new erosions and extensions of old ones, were quantified at 14 joints in each hand and wrist. Each of the joints was scored on an 8-point scale of 0 to 3.5, giving a maximum erosion score of 49 per hand and wrist, or 98 per patient. The maximum erosion score was normalized to 100. Thirteen joints were examined for joint space narrowing (JSN) and each joint was scored on a 9-point scale of 0 to 4.0, giving a maximum JSN score of 52 per hand and wrist, or 104 per patient. The maximum JSN score was normalized to 100, giving a maximum total normalized damage score of 200 per patient.

Statistical analysis. The 48-week change from baseline in radiographic progression was analyzed using a repeated-measure mixed model with fixed effects for treatment group, treatment group by study-week interaction, country, baseline total modified Sharp score, CRP, rheumatoid factor (RF) status, and presence of erosive disease at baseline. Patients that had a baseline radiograph and at least one post-baseline radiograph were eligible for inclusion in the analysis. Three patients had missing RF assessments and were therefore excluded from the mixed model analysis.

The change in radiographic progression in 2 consecutive 24-week treatment periods was calculated as the within-subject difference: (score at 12 mo – score at 6 mo) – (score at 6 mo – score at baseline). This endpoint compares the change in the rates of radiographic progression during the first and second 24-week periods. The differences were analyzed using a Wilcoxon signed-rank test. For the group of patients that switched from placebo to anakinra, an additional comparison was made to identify an anakinra treatment effect using each patient's experience in the first 24-weeks as a placebo comparison for their experience while receiving anakinra. Patients were required to have baseline, 24-week, and 48-week radiographs in order to be included in the analysis. Therefore, the analysis was limited to patients who completed both 24-week treatment periods. Four patients were excluded from the analysis due to missing radiographic scores at baseline or at 24 weeks.

Patients who were originally randomized to placebo (i.e., randomized to placebo for 24 weeks, then re-randomized to anakinra 30, 75, or 150 mg/day) did not receive the same treatment for the total 48 weeks of the trial. To overcome this limitation, an analysis was conducted using the change observed at 24 weeks in patients who received placebo to project the 48-week change they could have experienced if they had continued to

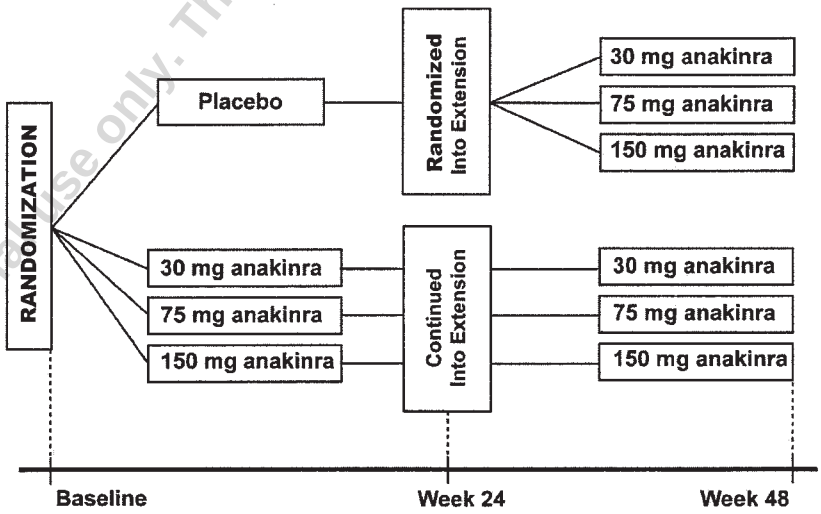

Figure 1. The 48-week study scheme. Patients were randomized to one of 4 treatment groups: placebo or anakinra 30 mg, 75 mg, or 150 mg/day. Upon completion of the 24-week placebo-controlled phase, patients entered a 24-week extension study. Patients receiving placebo were randomized to one of the 3 anakinra treatment groups; patients receiving treatment continued to receive the same anakinra dosage. Radiographs were obtained at baseline and at Weeks 24 and 48.

receive placebo. The radiographic progression during the second 24-week period was estimated using values from 100% (linear project) to 0% of the progression observed during the first 24-week period, recognizing that any value less than 100% is an attenuation of the progression observed during the first period. The estimated progression rates were similar to those observed elsewhere[2].

RESULTS

Patients' characteristics. A total of 472 patients were recruited; the majority were female Caucasians (Table 1). Disease duration was relatively short in each of the treatment groups (mean 3.7 to 4.3 yrs); measures of disease activity were high. More than 70% of patients had joint erosions at baseline. Eighty-two of 121 patients (67.8%) that received placebo completed the first 24 weeks of the study (Figure 2). Paired radiographs were available for analysis in 78 (95.1%). An adverse event was the reason for withdrawal in 24 (19.8%) and lack of efficacy in 11 (9.1%). Of the 351 patients that were randomized to receive anakinra, 263 (74.9%) completed the first 24 weeks. Paired radiographs were available in 251 (95.4%). An adverse event was the reason for withdrawal in 57 (21.7%) and lack of efficacy in 15 (5.7%). Three hundred nine patients (89.6% of the patients who completed the first phase) were enrolled into the second phase, and 218 (46.0% of those recruited to the first phase; 70.6% of those who completed) had a third radiograph at 48 weeks. In all, triplicate radiographs were available for analysis in 236 patients (50% of the number who were originally randomized into the first phase of the study), including 18 who withdrew from the study between Weeks 36 and 48 and underwent a final radiographic evaluation upon discontinuation. Triplicate radiographs (baseline, 24, and 48 weeks) were available for 58 (47.9%), 68 (57.2), 61 (52.6%), and 49 (42.2%) patients originally randomized to placebo and 30, 75, and 150 mg anakinra, respectively.

An adverse event and lack of efficacy were the reasons for withdrawal from the second phase in 46 (21.1%) and 26 (11.9%) patients, respectively.

Efficacy and adverse effects. The effects of anakinra on signs and symptoms of RA in this study have been described[11]. In brief, 43% of the patients who received 150 mg/day anakinra experienced an ACR 20 response at 24 weeks (the primary efficacy endpoint), compared to 27% of those who received placebo ($p = 0.014$). Of the patients who received 30 mg/day and 75 mg/day anakinra, 39% and 34%, respectively, achieved ACR 20 responses. These results were not significantly different from placebo. At 48 weeks, 44%, 53%, and 49% of the patients who continued to receive 30, 75, and 150 mg/day anakinra showed ACR 20 responses. Of the patients who had received placebo and were randomized to receive anakinra 30 (n = 30), 75 (n = 24), and 150 mg/day (n = 22) at 24 weeks, 50%, 44%, and 71%, respectively, had ACR 20 responses at 48 weeks.

Anakinra was well tolerated at doses of 30, 75, and 150 mg/day for up to 76 weeks[11]. An injection-site reaction was the most frequently observed adverse event during the first 24 weeks of treatment[7]. Most injection-site reactions were mild and transient, and resulted in withdrawal from the study in 5% of patients receiving 150 mg/day anakinra, compared to 2% of patients receiving placebo. In the extension phase, other adverse events resulting in withdrawal included leukopenia (1.6%) and infections (1.3%).

Table 1. Baseline patient characteristics by treatment group.

		Anakinra, mg/day			
	Placebo, n = 121	30, n = 119	75, n = 116	150, n = 116	All Anakinra, n = 351
Age, yrs, mean	52.2	53.3	52.6	54.2	53.4
Female, %	85 (70.2)	85 (71.4)	92 (79.3)	92 (79.3)	269 (76.6)
Caucasian, %	118 (97.5)	118 (99.2)	114 (98.3)	116 (100)	348 (99.1)
Duration of RA, yrs, mean (SD)	3.7 (2.4)	4.3 (2.2)	4.2 (2.4)	3.9 (2.5)	4.1 (2.4)
Rheumatoid factor positive, %	84 (69.4)	84 (70.6)	80 (69.0)	80 (69.0)	244 (69.5)
C-reactive protein, mg/dl, mean (SD)	4.3 (4.3)	4.1 (3.7)	4.1 (3.8)	4.0 (4.0)	4.1 (3.8)
ESR, mm/h, mean (SD)	47.1 (30.0)	49.3 (26.9)	53.1 (30.4)	48.6 (29.8)	50.3 (29.0)
Tender joint count (0-68), mean (SD)	33.0 (14.3)	33.4 (13.5)	35.6 (14.4)	35.3 (13.4)	34.8 (13.8)
Swollen joint count (0-66), mean (SD)	25.6 (10.3)	26.2 (9.9)	26.1 (10.2)	26.5 (9.5)	26.3 (9.8)
HAQ (0-3), mean (SD)	1.5 (0.6)	1.5 (0.6)	1.6 (0.7)	1.6 (0.7)	1.6 (0.7)
No. of previous DMARD, mean (SD)	1.3 (0.9)	1.3 (0.9)	1.3 (1.0)	1.2 (1.0)	1.3 (1.0)
NSAID use, %	106 (87.6)	95 (79.8)	97 (83.6)	96 (82.8)	288 (82.1)
Corticosteroid use, %	48 (39.7)	58 (48.7)	47 (40.5)	48 (41.4)	153 (43.6)
No. of patients with baseline and at least one post-baseline radiograph	79	87	88	79	254
No. of patients with 48 week radiographs	58	68	61	49	178
Modified Sharp total score, mean (SD)	27.1 (28.1)	29.1 (28.8)	27.9 (24.7)	24.5 (25.3)	27.3 (26.3)
Modified Sharp JSN score, mean (SD)	11.7 (14.2)	13.5 (14.6)	13.3 (13.8)	10.5 (12.2)	12.5 (13.7)
Modified Sharp erosion score, mean (SD)	15.4 (14.7)	15.6 (14.9)	14.6 (12.0)	14.0 (13.9)	14.8 (13.6)
Presence of erosive disease, %	90 (74.4)	91 (76.5)	86 (74.1)	80 (69.0)	257 (73.2)

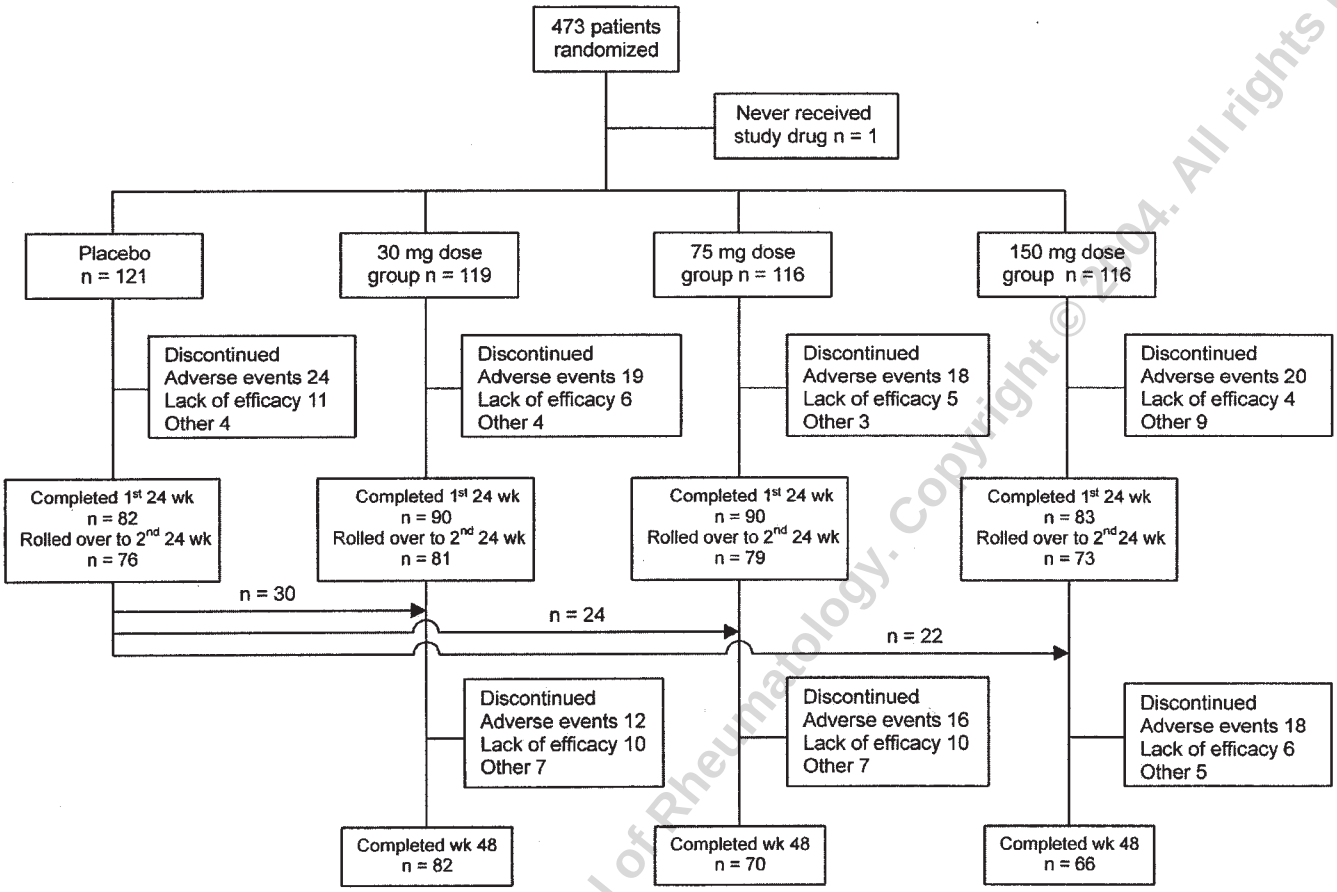

Figure 2. Randomization, withdrawal, and completion details of patients entering the study.

Radiographic evaluation of joint damage

Radiographic evaluation of joint damage after 48 weeks' treatment. A significant treatment effect was observed by Week 24 ($p = 0.001$; Figure 3). The mean change in the total modified Sharp score (TMSS) of 178 patients who completed 48 weeks' treatment with anakinra was 2.12, significantly less than 3.81 observed in 58 patients who were originally randomized to placebo ($p = 0.015$). The

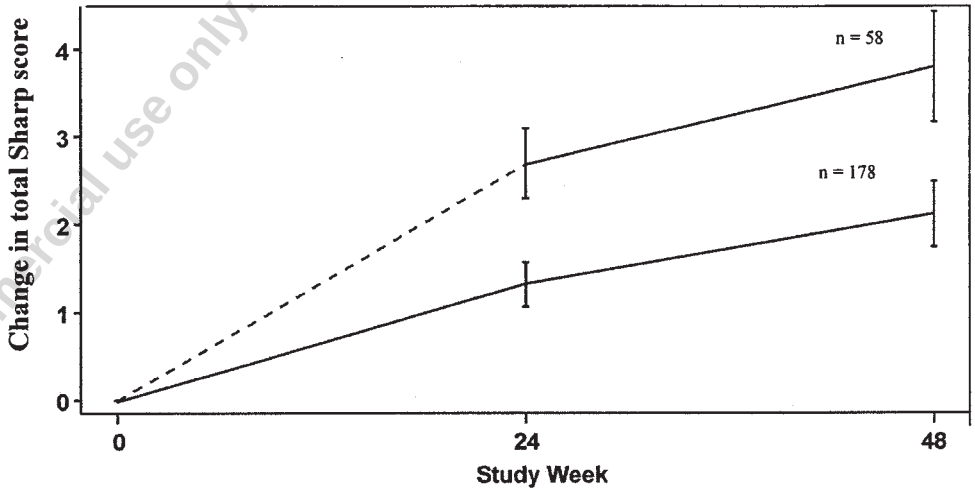

Figure 3. Changes from baseline of the modified total Sharp scores in patients randomized to placebo and all doses of anakinra. Broken line represents placebo treatment group; solid lines represent all anakinra dosage groups combined. Results at Weeks 24 and 48 are indicated. A repeated-measures mixed model was employed. Significant treatment effects were observed at Weeks 24 ($p = 0.001$) and 48 ($p = 0.015$).

change in TMSS observed in patients who received anakinra dosages 75 and 150 mg/day was also significantly less than in the patients who received placebo (Table 2). The mean change in the erosion score of patients who received anakinra treatment for 48 weeks was 1.15, which was significantly less than 2.03 observed in the patients originally randomized to placebo ($p = 0.006$). A significant reduction in the erosion score was observed with each of the 3 anakinra dosages. The mean change in the JSN score was 1.53 in placebo-treated patients, compared to 0.89 in anakinra-treated patients ($p = 0.084$).

To assess the robustness (relative to patients that withdrew early) of the observed results, the rate of progressive joint damage in the patients who continued into the extension phase was compared to the rate in patients who dropped out of the study at 24 weeks (data not shown). In the placebo group, the change in mean total Sharp score at 24 weeks in those who did not continue for a second 24 weeks was worse than the change in those who continued (4.21 compared to 3.41, respectively). In contrast, the change in the mean total Sharp score at 24 weeks in the patients who received anakinra and continued into the extension phase was greater than the mean change in those that did not continue (1.89 compared to 1.39, respectively). Although some of these samples were small, the trends suggest that the cohort of placebo-treated patients entering the extension study had less structural damage at 24 weeks than those who dropped out, and that the cohort of anakinra-treated patients who entered the extension phase had more joint damage than the dropouts.

Comparison of joint damage during the 2 consecutive 24-week study periods. To assess treatment effects for patients originally randomized to placebo and then to anakinra, an analysis of the 2 consecutive 24-week periods was conducted (Table 3, Figure 4). In the 58 patients who received placebo during the first 24 weeks, the change in TMSS was significantly reduced after randomization to anakinra treatment from 3.43 to 1.31 ($p < 0.001$; Table 3, Figure 4A). The median change was 1.95 following placebo, and 0 following the 24 week treatment period. Significant reductions were observed with each of the 3 dosages (Table 3). Significant reductions in both the erosion and JSN scores were also observed ($p < 0.001$; Table 3, Figures 4B, 4C). The median changes in the erosion and JSN scores during the first 24 weeks were 0.51 and 0.72, respectively, compared to median changes of 0 for each score during the second 24 weeks (Table 3, Figures 4B, 4C).

To assess whether treatment effects observed in the first 24 weeks of the study were durable, an analysis of the 2 consecutive treatment periods was conducted for patients originally randomized to receive anakinra. The 178 patients with a complete set of radiographs who completed 48 weeks of anakinra treatment showed a significant reduction in the TMSS from 1.82 after the first 24-week treatment period to 1.18 after the second ($p < 0.001$; Table 3, Figure 4A). The median change was 0.51 after the first treatment phase and 0 after the second. Significant reductions in the second 24-week period were observed after anakinra 75 mg/day ($p = 0.006$) and 150 mg/day ($p = 0.008$; Table 3). Similarly, a statistically significant reduction of the mean erosion score in the second treatment period was observed ($p < 0.001$; Figure 4B). The median changes in the erosion scores during the first 24 weeks were 0, 1.02, and 0 after 30, 75, and 150 mg/day, and 0 for each dose during the second 24 weeks (Table 3). The mean changes in the JSN scores in each of the 2 treatment periods were similar (Figure 4C). The median changes in the JSN scores were 0 for each of the treatment groups after each treatment period (Table 3).

Patients who were originally randomized to placebo were randomized to receive anakinra at 24 weeks. To emulate what would have happened if these patients had received placebo for the entire 48-week study period, an analysis of

Table 2. Modified Sharp scores: change from baseline at 48 weeks.

		Anakinra, mg/day			
	Placebo*, n = 79	30, n = 87	75, n = 88	150, n = 79	All Anakinra, n = 254
Score					
Adjusted mean	3.81	2.43	1.91	1.90	2.12
SE	0.63	0.59	0.62	0.61	0.38
p		0.099	0.025	0.025	0.015
Erosion					
Adjusted mean	2.03	0.88	1.18	1.21	1.15
SE	0.29	0.28	0.29	0.28	0.17
p		0.004	0.035	0.038	0.006
Joint space narrowing					
Adjusted mean	1.53	1.19	0.66	0.79	0.89
SE	0.32	0.30	0.31	0.32	0.18
p		0.423	0.048	0.096	0.084

* Patients in the placebo group received anakinra between Weeks 24 and 48.

Table 3. Modified Sharp scores: change in radiographic progression in 2 consecutive 24-week treatment periods.

First 24 Weeks	Placebo				30 mg	75 mg	150 mg	All Anakinra
Second 24 Weeks	30 mg	75 mg	150 mg	All Anakinra	30 mg	75 mg	150 mg	All Anakinra
Modified Sharp Score								
No. of subjects in analysis	19	20	19	58	68	61	49	178
Baseline to 24 weeks								
Mean	2.55	2.01	5.79	3.43	1.74	1.95	1.78	1.82
SD	4.81	3.03	6.56	5.18	2.75	2.29	3.30	2.76
Median	1.47	0.24	3.96	1.95	0.51	1.02	0.48	0.51
25th,	0.00	0.00	1.02	0.00	0.00	0.00	0.00	0.00
75th percentiles	1.98	2.75	7.05	3.96	2.97	3.45	1.98	3.06
24 weeks to 48 weeks								
Mean	1.10	0.88	1.99	1.31	1.61	0.95	0.85	1.18
SD	3.34	2.05	2.41	2.65	2.90	4.10	2.17	3.21
Median	0.00	0.00	1.50	0.00	0.00	0.00	0.00	0.00
25th,	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
75th percentiles	1.02	1.01	3.06	1.98	2.43	1.44	0.99	1.92
Difference								
Mean	–1.46	–1.13	–3.81	–2.11	–0.13	–1.00	–0.93	–0.65
SD	2.18	2.07	6.71	4.31	2.65	3.71	2.62	3.06
Median	–0.96	0.00	–1.89	–0.96	0.00	0.00	0.00	0.00
25th,	–1.98	–1.60	–4.08	–2.94	–1.02	–1.56	–1.50	–1.53
75th percentiles	0.00	0.00	0.00	0.00	0.06	0.00	0.00	0.00
p	0.008	0.010	0.002	< 0.001	0.282	0.006	0.008	< 0.001
Modified Sharp Erosion Score								
Baseline to 24 weeks								
Mean	1.26	1.43	3.06	1.91	1.06	1.49	1.19	1.24
SD	2.89	2.01	2.89	2.70	1.65	1.85	2.67	2.04
Median	0.51	0.00	2.04	0.51	0.00	1.02	0.00	0.00
25th,	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
75th percentiles	1.02	2.04	5.61	2.04	1.79	2.55	1.02	2.04
24 weeks to 48 weeks								
Mean	0.59	0.61	1.13	0.77	0.77	0.53	0.41	0.59
SD	2.04	1.73	1.72	1.82	1.64	1.76	1.05	1.55
Median	0.00	0.00	1.02	0.00	0.00	0.00	0.00	0.00
25th,	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
75th percentiles	0.51	0.26	1.53	1.02	1.02	0.51	0.00	0.51
Difference								
Mean	–0.67	–0.82	–1.93	–1.13	–0.29	–0.96	–0.78	–0.65
SD	1.22	1.49	2.51	1.88	1.54	1.87	2.20	1.87
Median	0.00	0.00	–1.02	0.00	0.00	0.00	0.00	0.00
25th,	1.02	–1.53	–3.57	–1.53	–0.51	–1.53	–1.02	–1.02
75th percentiles	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
p	0.004	0.023	0.002	< 0.001	0.129	< 0.001	< 0.001	< 0.001
Modified Sharp Joint Narrowing Score								
Baseline to 24 weeks								
Mean	1.29	0.58	2.73	1.52	0.69	0.47	0.59	0.58
SD	2.07	1.22	4.75	3.13	1.55	0.87	1.20	1.25
Median	0.96	0.00	1.44	0.72	0.00	0.00	0.00	0.00
25th,	0.00	0.00	0.96	0.00	0.00	0.00	0.00	0.00
75th percentiles	0.96	0.48	3.37	1.44	1.20	0.96	0.96	0.96
24 weeks to 48 weeks								
Mean	0.51	0.26	0.86	0.54	0.84	0.43	0.44	0.59
SD	1.71	0.98	1.26	1.34	1.60	2.55	1.47	1.95
Median	0.00	0.00	0.48	0.00	0.00	0.00	0.00	0.00
25th,	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
75th percentiles	0.00	0.00	0.96	0.96	0.96	0.48	0.48	0.96
Difference								
Mean	–0.78	–0.31	–1.87	–0.98	0.16	–0.04	–0.15	0.01
SD	1.31	1.55	4.98	3.10	1.95	2.49	1.42	2.03
Median	–0.96	0.00	–0.00	0.00	0.00	0.00	0.00	0.00
25th,	–0.96	–0.24	–1.92	–0.96	–0.48	0.00	–0.48	–0.48
75th percentiles	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
p	0.021	0.297	0.040	< 0.001	0.513	0.696	0.458	0.620

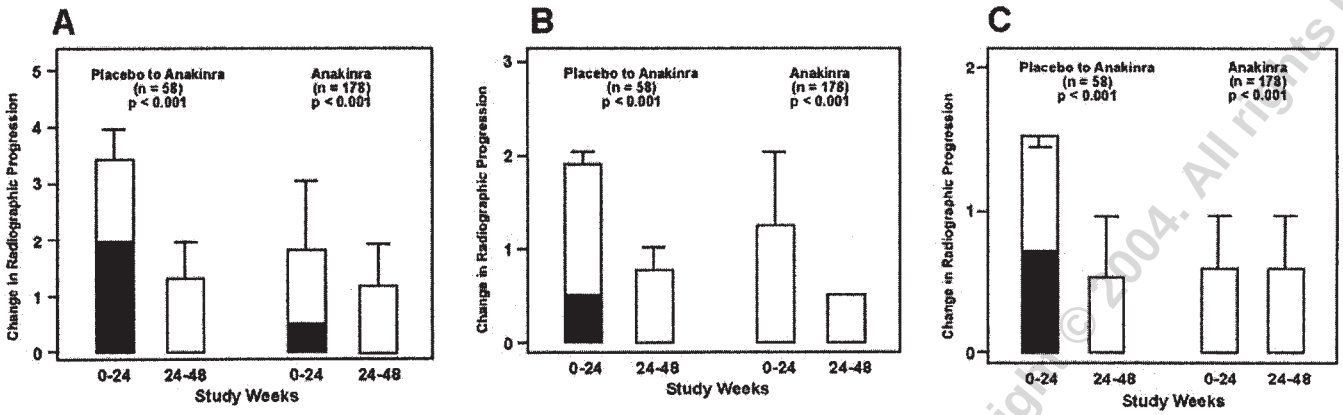

Figure 4. Changes from baseline of the total modified Sharp scores (A), modified Sharp erosion scores (B), and modified Sharp joint space narrowing scores (C) in the two 24-week treatment periods. Changes observed in patients randomized to placebo (Week 0 to 24) are compared to changes in the same patients after randomization to all doses of anakinra (Week 25 to 48). Similarly, changes observed in patients randomized to all doses of anakinra (Week 0 to 24) are compared to changes in the same patients during the second 24-week treatment period (Week 25 to 48). Columns represent the mean changes, the whiskers the 75% quartiles; black bars represent median values.

the TMSS compared the observed changes after 48 weeks of anakinra treatment with predicted changes in the placebo-treated patients, if they had continued to receive placebo for the entire 48 weeks (Figure 5). If treatment with placebo had continued for 48 weeks, the predicted change from baseline of the TMSS that assumed radiographic joint damage continued to progress at the same rate as that observed at 24 weeks was significantly different from the change observed in patients that received anakinra ($p < 0.001$). To assess the robustness of the comparison with the predicted change in TMSS, the predicted change from baseline in the patients who received placebo could have been attenuated by up to 40% of the rate observed at 24 weeks before crossing the significance threshold of 0.05 from the rate observed in patients who received anakinra (actual $p = 0.039$).

Patients with established erosions at baseline. Altogether, 347 patients had established joint erosions at baseline. Seventy-four of 257 (28.8%) who had received anakinra, and 15 of 90 (16.6%) who had received placebo, showed no further evidence of joint damage after 24 weeks ($p = 0.022$; Table 4). Statistically significant differences were observed between patients who received placebo and anakinra 30 and 150 mg/day. No new joint erosions were identified in 35.0% of the patients receiving anakinra, compared to 22.2% of the patients receiving placebo ($p = 0.020$). Statistically significant differences were also observed between placebo and anakinra 30 and 150 mg/day. Finally, no further JSN occurred in 40.5% of patients receiving anakinra, or in 22.2% of patients receiving placebo ($p < 0.001$). Statistically significant differences between placebo and each of the anakinra doses were observed.

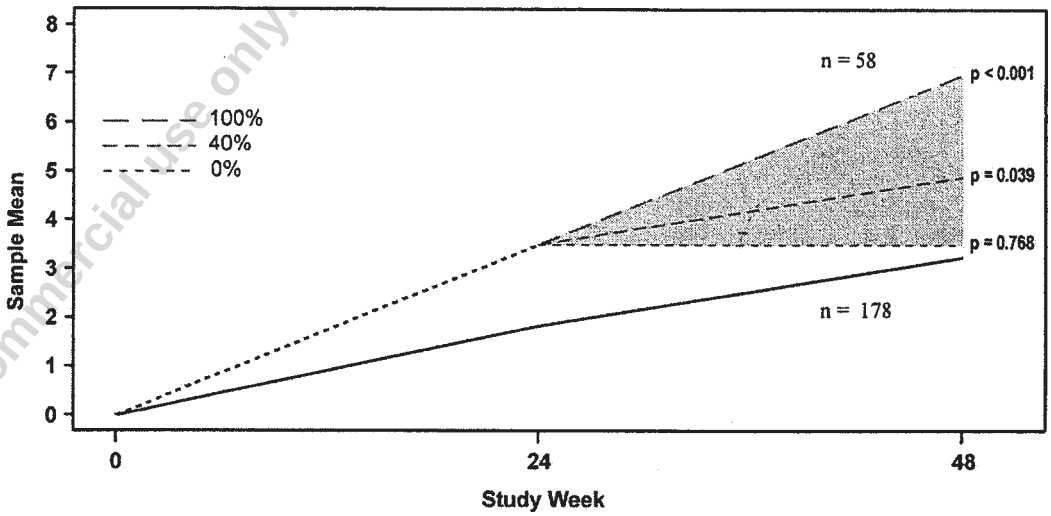

Figure 5. Comparison between observed change from baseline of the modified total Sharp score after 48 weeks' treatment and projected damage in patients who received placebo. Broken lines represent placebo treatment group; solid line represents all anakinra dosage groups combined. A modified intention-to-treat analysis was used.

Table 4. Arrest of joint damage in patients with baseline erosions.

	Placebo, n = 90	Anakinra, mg/day 30, n = 91	75, n = 86	150, n = 80	All Anakinra, n = 257
Total score					
n (%)	15 (16.7)	28 (30.8)	21 (24.4)	25 (31.3)	74 (28.8)
Odds ratio		2.24	1.57	2.43	2.07
p		0.026	0.234	0.022	0.022
Erosion					
n (%)	20 (22.2)	35 (38.5)	25 (29.1)	30 (37.5)	90 (35.0)
Odds ratio		2.22	1.42	2.36	1.98
p		0.017	0.318	0.021	0.020
Joint space narrowing					
n (%)	19 (21.1)	36 (39.6)	35 (40.7)	33 (41.3)	104 (40.5)
Odds ratio		2.47	2.60	2.86	2.70
p		0.006	0.004	0.003	< 0.001

DISCUSSION

The patients recruited to this study had severe RA with high measures of disease activity. Most had failed previous DMARD therapy. Those randomized to receive placebo had a mean disease duration of 3.7 years and a mean total modified Sharp score of 27.1 at baseline, suggesting that the joint damage score had increased by a mean of 7.3 per year. The score in the placebo group increased by a further 3.4 after 24 weeks, indicating that the rate of joint damage progression in this cohort remained constant. This represents a rate of joint damage that was 3.7% of the maximum score of 200 per year, and is consistent with severe RA. In a large 19-year prospective study, the mean total Sharp score increased constantly by 6.6 per year in the cohort of patients with an ESR > 30 mm/h, which represented a rate of joint damage that was 2% of the maximum score of 330 employed in the study[2].

The patients who were treated with anakinra for 48 weeks developed significantly less joint damage than patients originally randomized to placebo. The treatment effect was greatest in patients who received the larger doses of 75 and 150 mg/day. Based on the measurements of joint damage observed during the placebo phase, it was possible to predict that the difference between placebo and anakinra treatment would have remained statistically significant at 48 weeks, even if the rate of joint damage in the placebo group had diminished to only 40% of the rate observed at 24 weeks. Patients who received anakinra for 48 weeks showed significantly less joint damage during the second 24-week treatment period than the first, indicating that the benefits of treatment with anakinra increased over time. The enhanced slowing of joint damage during the second 24-week treatment period was observed for each of the 3 treatment dosages, and was due to the potent beneficial effects of treatment on the formation of new erosions. The effect of anakinra on progressive joint damage during the second 24-week treatment period was highlighted by observing an arrest for both median JSN and erosion scores for each of the 3 treatment dosages. Further analyses of the patients with established joint erosions at baseline suggested that apparent arrest of progressive joint damage was also more likely to occur in the patients who received anakinra.

Of the 351 patients who were initially randomized to any dose of anakinra, 233 (66.4%) entered the 24-week extension phase. Similarly, 62.8% of the 121 patients who were initially randomized to placebo were randomized to anakinra at 24 weeks, and remained in the study. The number of dropouts, and the incomplete sets of radiographs, may have had an effect on the analysis of the extension phase. The placebo-controlled study was not originally designed or powered to perform an analysis of joint damage in the extension study. Another limitation of the extension study was the absence of a placebo group. The maintenance of placebo for 48 weeks was not ethically justified. It is also possible that the crossover at 24 weeks might have introduced some selection bias, with the better anakinra responders remaining in the study and the poor responders dropping out. However, it appears unlikely from the data that the beneficial effects of anakinra that were observed in the 48-week mixed model analysis resulted from a selection bias. Indeed, the results suggest that any possible selection bias was in the opposite direction, resulting in a bias against finding a positive treatment effect. Nevertheless, these possible limitations must be considered when interpreting the results.

Several studies of nontargeted therapies have demonstrated significant retardation of joint damage in RA[13-18]. The protective effects of TNF-α-targeted therapies on joint damage have been described in patients receiving infliximab[19] and etanercept[20,21]. It is difficult to directly compare the effects of anakinra with TNF-α-targeted therapies, due to considerable differences in protocol designs, patient

selection, and outcome measures in each of the published studies. For example, the patients recruited to the infliximab study had a mean disease duration of 12 years, and received methotrexate in combination with infliximab or placebo[19]. Patients recruited to the etanercept study had a mean disease duration of only one year, and were randomized to receive either etanercept or methotrexate in monotherapeutic regimes[20]. In both studies, the measures of joint damage were derived from the radiographic evaluation of both hands and feet, using scales of 0 to 440 and 398, respectively. In contrast, the modified Sharp scores employed in the present study were derived from the radiographic evaluation of hands only, using a scale of 0 to 200. Nevertheless, taken together, these studies indicate that both TNF-α and IL-1-targeted therapies have important modulatory effects on the disease mechanisms that are associated with structural damage of bone and cartilage in RA.

APPENDIX

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