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ORIGINAL ARTICLE

Intraarticular Injection of Anakinra in Osteoarthritis of the Knee: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study

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Objective. **To evaluate the clinical response, safety, and tolerability of a single intraarticular injection of anakinra in patients with symptomatic osteoarthritis (OA) of the knee.**

Methods. **Patients with OA of the knee were enrolled in a multicenter, double-blind, placebo-controlled study and randomized 2:1:2 to receive a single intraarticular injection of placebo, anakinra 50 mg, or anakinra 150 mg in their symptomatic knee. Patients were evaluated for 12 weeks postinjection. The primary end point was the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score from baseline to week 4. Safety assessments included the evaluation of adverse events (AEs), laboratory tests, and vital signs. Pharmacokinetic parameters were assessed in a subset of patients.**

Results. **Of 170 patients who enrolled, 160 (94%) completed the study. The mean improvements from baseline to week 4 in the WOMAC score were not statistically different between the placebo group and the patients who received 50 mg of anakinra ($P = 0.67$) or 150 mg of anakinra ($P = 0.77$). Anakinra was well tolerated. No withdrawals due to AEs or serious AEs, and no serious infections or deaths were reported. No clinically significant trends were noted in laboratory values or vital signs. Pharmacokinetic parameters demonstrated that the mean terminal half-life of anakinra in serum after intraarticular injection was ~4 hours.**

Conclusion. **Anakinra was well tolerated as a single 50-mg or 150-mg intraarticular injection in patients with OA of the knee. However, anakinra was not associated with improvements in OA symptoms compared with placebo.**

INTRODUCTION

Osteoarthritis (OA) is a common rheumatic condition often affecting women and the elderly (1–3). OA is primarily characterized by chronic pain and joint disease and also by cartilage degradation and loss, subchondral bone remodeling, and varying degrees of synovial inflammation.

The exact cause of OA is unknown, and currently no disease-modifying therapies exist. Guidelines for management of OA of the hip and knee have been recommended by international conference consensus (4–7). These include nonpharmacologic therapies (reduction of biomechanical dysfunction and other modifiable risk factors), occupational and physical therapy, pharmacologic therapies (topical analgesics, nutritional supplements [glucosamine, chondroitin sulfate], oral analgesics, nonsteroidal antiinflammatory drugs [NSAIDs]), and injected corticosteroids or hyaluronate viscosupplementation (4–7). Because of progression in cartilage defects, surgical

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joint replacement is generally the end-stage therapy for OA (8–10). Therefore, a clear need exists for new OA therapies.

Cytokines such as interleukin-1 (IL-1) may play a pivotal role in OA by stimulating the synthesis of proteolytic enzymes, cytokines, nitric oxide, prostaglandins, and other mediators and effectors of tissue inflammation and destruction (11–13). Evidence of the beneficial role of IL-1 receptor antagonist (IL-1Ra) was first demonstrated in patients with rheumatoid arthritis (14,15). Systemic anakinra, a recombinant form of IL-1Ra, can reduce joint inflammation and slow the erosive course of the disease (15). In vitro and animal models of OA suggest that anakinra might have beneficial effects on symptoms and structural modifications in OA. In these studies, intraarticular administration was preferred to reach the damaged cartilage. In a study investigating the effect of recombinant human IL-1Ra (rHuIL-1Ra) in a canine experimental OA model, rHuIL-1Ra (2 mg or 4 mg twice weekly for 4 weeks) or placebo was injected in the knees of dogs (16). Significant dose-dependent reductions in the number and size of osteophytes and cartilage lesions were observed in the groups injected with anakinra. A significant reduction in collagenase 1 expression in cartilage was also noted, providing evidence for a role of IL-1 in cartilage degradation.

Two additional animal studies demonstrated the beneficial effect of IL-1Ra in OA, using gene transfer therapy methodology (17,18). Compared with control groups, groups treated with IL-1Ra had less severe cartilage lesions, a significant reduction in the size of osteophytes and macroscopic and histologic lesions, and significant improvements in clinical indicators of pain and disease activity, cartilage preservation, and synovium and articular cartilage histology.

A pilot clinical study performed to investigate the tolerability of intraarticular injections of anakinra in 13 patients with OA of the knee demonstrated that anakinra at a dose of 150 mg was well tolerated and suggested that pain and function measurements improved (19).

The purpose of this study was to evaluate the efficacy and safety of an intraarticular injection of anakinra in patients with OA of the knee. It was hypothesized that intraarticular anakinra would be safe and well tolerated in patients with OA of the knee, and would provide a superior and sustained clinical effect compared with placebo.

PATIENTS AND METHODS

Patients. Patients age ≥18 years were eligible for enrollment if a diagnosis of OA in the index knee (in patients with bilateral knee OA, the more symptomatic knee was used) was present, as determined by the American College of Rheumatology (formerly the American Rheumatism Association) criteria (20), with pain in the index knee defined as a level >30 mm on a 100-mm visual analog scale (VAS). Radiographic evidence of tibiofemoral compartment OA of the index knee within 12 months before screening was also required. Active effusion or inflammatory flare could not be present, and NSAIDs were to be discontinued 3 days before study baseline. Doses of any nonprescribed supplements, including glucosamine or chondroitin sulfate, shark cartilage, diacerhein, or soya extract, as well as use of physical therapy, biomechanical devices, or orthotic supports, were required to be stable for at least 2 months before screening.

Patients were excluded for isolated patellofemoral OA in the index knee, inflammatory arthropathy or secondary OA, Kellgren/Lawrence (K/L) grade 4 OA in the index knee, hip OA ipsilateral to the index knee, any prior intraarticular injection with anakinra or experimental therapy, intraarticular corticosteroid injection in the prior 1 month, viscosupplementation within the prior 3 months, active infection or a history of recurrent or chronic infection, pregnancy, significant medical conditions including malignancy within the previous 5 years, or contraindications to knee injection.

During the study, patients were prohibited from receiving NSAIDs, intraarticular injections (including corticosteroids and hyaluronic acid), systemic corticosteroids, subcutaneous anakinra, or grade 3 analgesics (morphine). In addition, changes in the use of physical therapy, biomechanical devices, or orthotic supports were prohibited. The only rescue analgesic allowed was acetaminophen at a dosage of ≤4 gm/day.

Written informed consent was obtained from the patients before study enrollment. Patients who withdrew from the study were not replaced.

Study design. This multicenter, double-blind, placebo-controlled, parallel-dosing study was designed to evaluate changes in symptoms, as assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (21), from baseline to week 12, in patients with knee OA after receiving an intraarticular injection of anakinra or placebo. The study was conducted at 20 study centers in 3 countries (France, US, and Canada) in accordance with the Declaration of Helsinki, the US Food and Drug Administration, and the International Conference on Harmonisation Guidelines on Good Clinical Practice. An Independent Ethics Committee or Institutional Review Board at each study center reviewed and approved the study protocol, the informed consent form, and all other subject or recruitment information.

After a 2-week screening period, patients were eligible for study entry. Patients were randomized 2:1:2 to receive a single intraarticular injection of placebo, 50 mg of anakinra, or 150 mg of anakinra in the index knee. Study assessments were performed at the time of screening, at baseline, on day 4, and at weeks 4, 8, and 12.

Study medication. Anakinra was provided in 100-mg/ml vials containing 100 mg of anakinra, 10 m*M* sodium citrate, 140 m*M* sodium chloride, 0.5 m*M* EDTA, 0.1% (weight/weight) polysorbate 80, and water for injection in a quantity sufficient to yield 1 ml final volume. The placebo formulation was the same, but without the addition of anakinra. A 1.5-ml syringe was prepared, irrespective of the dose, by an unblinded pharmacist or qualified person. Treatment was administered under aseptic conditions by the investigator or his/her designee.

Procedures and end points. An interactive voice response system (IVRS; Clinphone, Nottingham, UK) was used to randomize patients to the placebo, anakinra 50 mg, or anakinra 150 mg group. Randomization occurred during the baseline visit and was not randomized in blocks according to the study center. Blinding was maintained by providing placebo and anakinra (50 mg or 150 mg) in identical containers. At each site, authorized staff had unique Personal Identification Numbers to access the IVRS if unblinding was essential for the clinical management of the patient. Unblinding for any other reason was considered a protocol deviation.

The primary efficacy end point was the change in WOMAC score from baseline to week 4. The WOMAC is a questionnaire that assesses pain, stiffness, and physical function. The total WOMAC score (range 0–2,400) is a summation of the scores for each individual domain (pain 0–500, stiffness 0–200, and physical function 0–1,700). Secondary efficacy end points included the change from baseline at each postbaseline visit in the WOMAC score and in scores of the 3 WOMAC domains, as well as achievement of ≥50% improvement from baseline in the WOMAC score.

Additional efficacy assessments used a 100-mm VAS to assess the change from baseline in the patient's assessment of pain activity and the patient's global assessment of disease activity, and a 0–4-point Likert scale to assess the change from baseline in the physician's global assessment of disease activity. Responder status, as defined by the Outcome Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) criteria, was also analyzed (22).

Exploratory end points included the amount of rescue analgesic used and time to NSAID/analgesic reintroduction. Patient outcome data at weeks 4, 8, and 12 were explored; these data included change from baseline in hours of lost productivity as measured by the Health-Related Productivity Questionnaire (HRPQ), the health utility score using the EuroQol-5D (EQ-5D), each of the 8 scales in the Short Form 36 (SF-36), and the physical and mental component scales of the SF-36.

Cleavage products or propeptides in collagen synthesis (846-epitope [ng/ml]), type II collagen levels (μg/liter), and urinary C-telopeptide of type II collagen (CTX-II) levels (ng/mmoles) were measured to determine whether patients with rapid disease progression or early evidence of protective or modifying effects in preserving cartilage could be identified. Serum and urine samples were collected at baseline and weeks 4 and 12 to measure cartilage or bone turnover. Samples were processed and analyzed at CCBR (Immunodiagnostic Systems Limited, UK).

Safety end points included adverse events (AEs), serious AEs, infections, serious infections, and changes in hematologic and laboratory chemistries. Laboratory chemistries were evaluated using the National Cancer Institute Common Toxicity Criteria, version 2.0 (URL: http://www.fda.gov/cder/cancer/toxicityframe.htm). The tolerability of anakinra administered via intraarticular injection into the index knee was assessed with a retrospective analysis of AEs related to the injection method.

Statistical analyses. The sample size calculation was based on the first 12 weeks of the study. Given an expected difference in means divided by a within-group SD of 0.60 between the placebo and anakinra 150 mg groups, a sample size of 66 patients per arm provided at least 90% power to detect a statistically significant difference using a step-down method and Wilcoxon's rank sum test. In all patients who were randomized and received a study drug (either anakinra or placebo), efficacy and safety were analyzed according to their randomized treatment arm.

Fisher's exact test was used to compare proportions of dichotomous variables between treatments. Comparisons of distribution location parameters (for continuous and ordinal variables) between treatment arms were made using Wilcoxon's rank sum test. The log rank test was used to compare time-to-event data between treatment arms. Statistical significance was set at the 5% level. Missing data from the primary efficacy end points were imputed for primary analyses, using the last observation carried forward method. Changes in WOMAC scores were summarized by treatment arm; overall hypothesis testing was performed with a step-down method and Wilcoxon's rank sum test.

Secondary and exploratory end points were provided as descriptive summaries, with no formal hypothesis testing. No interim analyses were performed, and no changes were made to the statistical methods.

Pharmacokinetic analysis. Measurement of serum pharmacokinetics at 12 hours and on day 2 was planned in up to 30 patients, to assess the systemic distribution of anakinra and determine the mean residence time following intraarticular injection.

Noncompartmental analysis was performed on individual serum anakinra concentrations to estimate the maximum observed serum concentration (C_{max}) and the time when it occurred (T_{max}) after dosing. The area under the serum concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-}t}$) was estimated using the linear/log trapezoidal method. The area under the serum concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$) was calculated by summing the values for $AUC_{0\text{-}t}$ and $AUC_{t\text{-}inf}$. The apparent clearance (CL/F) was calculated as Dose/$AUC_{0\text{-}inf}$, and the terminal half-life ($t_{1/2,z}$) was calculated by ln(2)/λz. The mean residence time from time zero to infinity ($MRT0\text{-}_{inf}$) was computed as $AUMC_{0\text{-}inf}/AUC_{0\text{-}inf}$. $AUMC_{0\text{-}inf}$ was the area under the first moment curve extrapolated to infinity. $AUC_{t\text{-}inf}$ was estimated by dividing the observed concentration at the time of the last quantifiable concentration by the rate constant for the terminal log-linear phase of the concentration-time curve (λz).

RESULTS

doses of 50 and 150 MG

Text

Patient characteristics. Of the 170 patients who enrolled in the study, 69 received placebo, 34 received anakinra at a dose of 50 mg, and 67 received anakinra at a dose of 150 mg. A total of 160 patients (94%) completed the study, and 10 patients (6%) withdrew prematurely. The

Table 1. Baseline patient demographics of subjects who were randomized and received 1 dose of anakinra (50 mg or 150 mg) or placebo*

	Placebo (n = 69)	Anakinra 50 mg (n = 34)	Anakinra 150 mg (n = 67)	Total (n = 170)
Sex				
Male	25 (36)	17 (50)	21 (31)	63 (37)
Female	44 (64)	17 (50)	46 (69)	107 (63)
Ethnicity				
White	61 (88)	30 (88)	58 (87)	149 (88)
Black	1 (1)	2 (6)	0 (0)	3 (2)
Hispanic/Latino	7 (10)	2 (6)	8 (12)	17 (10)
Asian	0 (0)	0 (0)	1 (1)	1 (1)
Age, mean ± SD years	62.2 ± 10.0	63.3 ± 9.8	62.6 ± 9.4	62.6 ± 9.7
Range, years	34–82	36–80	41–85	34–85
Weight, mean ± SD kg	83.3 ± 17.4	81.5 + 17.6	86.2 ± 20.4	84.1 ± 18.6
Range, kg	49.0–133.0	51.0–120.3	52.7–160.0	49.0–160.0
Used corticosteroids	7 (10)	2 (6)	8 (12)	17 (10)
Used analgesics†	2 (3)	1 (3)	2 (3)	5 (3)
Used NSAIDs	43 (62)	18 (53)	40 (60)	101 (59)

* Values are the number (percentage) unless indicated otherwise. NSAIDs = nonsteroidal antiinflammatory drugs.
† Acetaminophen only.

most common reasons for withdrawal were protocol deviations (2 in the anakinra 50 mg group, 3 in the anakinra 150 mg group, 1 in the placebo group) and withdrawal of consent (n = 5). No patients withdrew due to AEs, and the protocol deviations did not result in any changes to study results.

Baseline demographics and prior OA medication use were similar among treatment groups (Table 1). Most patients were women (63%) and white (88%); the mean age was 62 years. Corticosteroids had been used by 10% of patients, analgesics by 3%, and NSAIDs by 59%.

Patients' baseline assessments of disease were consis-

Table 2. Disease measures at baseline for subjects who were randomized and received 1 dose of anakinra (50 mg or 150 mg) or placebo*

	Placebo (n = 69)	Anakinra 50 mg (n = 34)	Anakinra 150 mg (n = 67)	Total (n = 170)
OA duration, years	6.0 ± 6.2	8.1 ± 9.8	5.2 ± 5.7	6.1 ± 6.9
Range	0.02–39.0	0.01–41.0	0.01–29.0	0.01–41.0
Kellgren/Lawrence score, n (%)				
1	0 (0)	0 (0)	3 (4)	3 (2)
2	27 (39)	16 (47)	25 (37)	68 (40)
3	42 (61)	18 (53)	39 (58)	99 (58)
Total WOMAC score (0–2,400)†	1,282.2 ± 464.4	1,208.5 ± 495.7	1,329.2 ± 542.8	1,285.8 ± 502.2
Range	194.0–2,113.0	342.1–2,273.0	86.0–2,273.0	86.0–2,273.0
WOMAC pain (0–500)‡	258.4 ± 96.8	238.1 ± 98.7	265.7 ± 111.8	257.2 ± 103.3
Range	63–433	64–412	18–473	18–473
WOMAC stiffness (0–200)	111.9 ± 42.2	102.0 ± 46.5	115.3 ± 53.7	111.3 ± 47.8
Range	28–200	1–184	7–196	1–200
WOMAC physical function (0–1,700)§	910.9 ± 345.9	868.4 ± 367.1	948.2 ± 389.8	917 ± 367.1
Range	75–1,500	188.1–1,484	55–1,621	55–1,621
Physician global assessment (0–4)	2.4 ± 0.6	2.5 ± 0.6	2.3 ± 0.8	2.4 ± 0.7
Range	1–4	2–4	0–4	0–4
Subject global assessment (0–100)	55.7 ± 21.1	52.6 ± 18.4	57.1 ± 23.6	55.6 ± 21.6
Range	6–99	19–85	1–98	1–99
Subject assessment of pain (0–100)	51.2 ± 21.7	48.6 ± 22.1	54.2 ± 24.0	51.9 ± 22.7
Range	6–98	3–88	4–97	3–98

* Values are mean ± SD unless indicated otherwise. OA = osteoarthritis; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
† Based on 166 total patients (66 placebo, 34 anakinra 50 mg, 66 anakinra 150 mg)
‡ Based on 169 total patients (68 placebo, 34 anakinra 50 mg, 67 anakinra 150 mg)
§ Based on 167 total patients (67 placebo, 34 anakinra 50 mg, 66 anakinra 150 mg)

ranges show no dif!!!

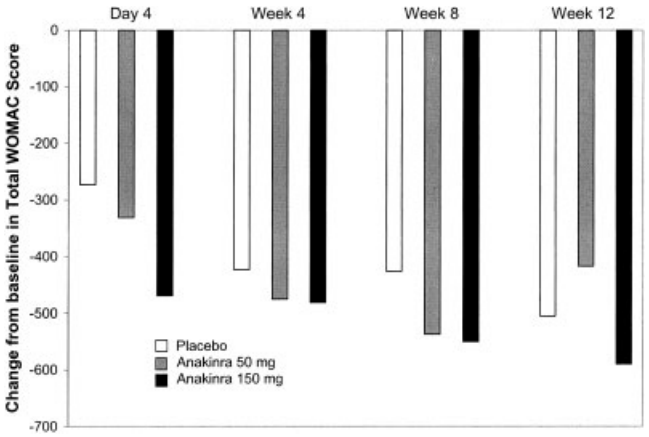

Figure 1. Mean change of total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score for the placebo group, the group receiving 50 mg of anakinra, and the group receiving 150 mg of anakinra.

tent with protocol criteria (Table 2). The mean duration of OA was 6 years across treatment groups. Patients had a mean baseline total WOMAC score of 1,286, a mean physician's global assessment score of 2.4, a mean patient's global assessment of disease activity score of 55.6, and a mean pain score of 51.9. Forty percent of patients had K/L grade 2 OA and 58% had K/L grade 3 OA.

Efficacy. All 3 treatment groups improved with respect to a decrease from baseline to week 4 in the WOMAC score (the primary efficacy end point). Improvement was greatest in the anakinra 50 mg group and smallest in the placebo group, although the differences between placebo (−407.1) and anakinra 50 mg (−475.4; $P = 0.67$) and between placebo and anakinra 150 mg (−475.1; $P = 0.77$) were not statistically significant. Similar improvements from baseline were observed at all other time points (Figure 1).

Secondary end points demonstrated the same trend, with improvements reported in all groups at all time points (Figure 2 and Table 3). No significant differences were seen in changes from baseline in the 3 WOMAC domains (Figure 2), patient's assessment of pain, patient's global assessment of disease activity, or the physician's global assessment. However, differences in the results for the WOMAC pain subscore in the anakinra 150 mg group versus the placebo group approached statistical significance on day 4 ($P = 0.051$). The results for responders (percentage of patients achieving ≥50% improvement in the WOMAC score or meeting the criteria for an OMERACT-OARSI responder) were also similar between treatment groups. Detailed results for responders are shown in Table 3.

Modest improvements in the HRPQ score, the SF-36 score (including physical and mental components), and the EQ-5D score were seen in all treatment groups. The amount of rescue analgesic used, as well as the time to NSAID reintroduction and rescue analgesic reintroduction, was also similar in all groups. Measures of cartilage degradation (846-epitope, type II collagen, and urinary CTX-II) showed little change during the study and no differences between treatments.

Pharmacokinetics. Serum anakinra concentrations were analyzed in 15 of 170 patients. All predose samples and all samples from patients receiving placebo (n = 4) were below the quantification limit (lower limit of quantitation = 40 ng/ml). The mean ± SD serum concentration-time profiles for the anakinra 50 mg group (n = 3) and anakinra 150 mg group (n = 8) are shown in Figure 3.

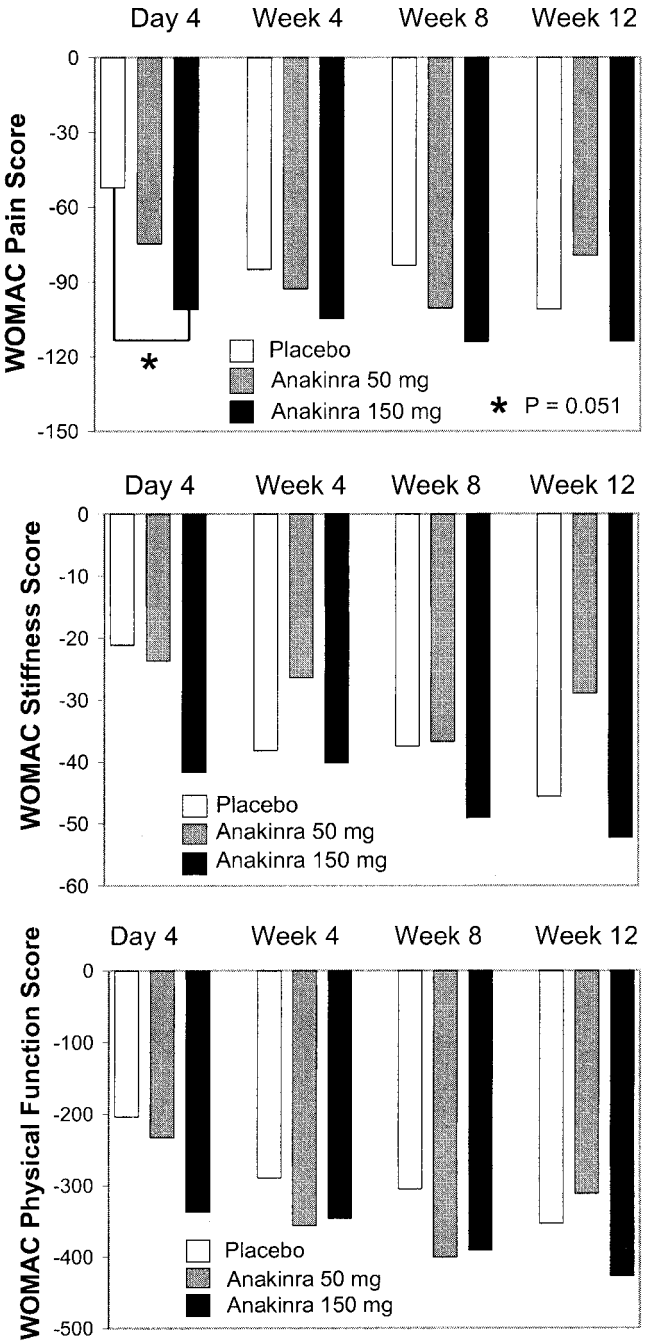

Figure 2. Mean change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscale score domains for pain (**top**), stiffness (**middle**), and physical function (**bottom**) from baseline.

Table 3. Assessments of efficacy by study visit for subjects who were randomized and received 1 dose of anakinra (50 mg or 150 mg) or placebo*

	Placebo (n = 69)	Anakinra 50 mg (n = 34)	Anakinra 150 mg (n = 67)
Subject assessment pain			
Day 4	−15.4 ± 29.4	−18.5 ± 28.7	−25.6 ± 24.4
Week 4	−21.7 ± 26.2	−24.1 ± 26.0	−26.2 ± 27.5
Week 8	−20.7 ± 28.5	−27.3 ± 29.9	−24.5 ± 29.1
Week 12	−23.6 ± 26.9	−18.9 ± 31.1	−27.8 ± 27.7
Subject global assessment			
Day 4	−12.7 ± 29.2	−15.3 ± 21.8	−24.7 ± 23.6
Week 4	−20.3 ± 26.3	−17.5 ± 28.5	−24.4 ± 25.9
Week 8	−20.7 ± 27.6	−21.2 ± 29.7	−24.1 ± 27.1
Week 12	−22.6 ± 26.8	−13.8 ± 28.6	−23.0 ± 31.1
Physician global assessment			
Day 4	−0.6 ± 0.9	−0.9 ± 1.1	−0.8 ± 0.9
Week 4	−0.9 ± 1.0	−1.0 ± 1.2	−0.7 ± 1.0
Week 8	−0.9 ± 1.2	−1.0 ± 1.2	−0.9 ± 1.1
Week 12	−1.0 ± 1.2	−0.8 ± 1.1	−0.8 ± 1.1
WOMAC ≥50% improvement, no.(%)			
Day 4	14 (20)	7 (21)	19 (28)
Week 4	23 (33)	14 (41)	25 (37)
Week 8	24 (35)	16 (47)	27 (40)
Week 12	28 (41)	14 (41)	30 (45)
OMERACT-OARSI responder, no. (%)			
Day 4	38 (55)	23 (68)	44 (66)
Week 4	39 (57)	21 (62)	44 (66)
Week 8	44 (64)	20 (59)	40 (60)
Week 12	45 (65)	21 (62)	41 (61)

* Values are mean ± SD unless indicated otherwise. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; OMERACT-OARSI = Outcome Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society International.

Serum anakinra concentrations following the single intraarticular injection were quantifiable through 12 hours postdose for all anakinra patients analyzed; 2 patients who received 150 mg of anakinra had quantifiable concentrations through 24 hours postdose. The median T_{max} was 2 hours for both anakinra groups. The mean C_{max} and $AUC_{0\text{-inf}}$ values appeared to be dose proportional, and mean clearance/filtration values were similar (anakinra 50 mg group, 245 ml/minute; anakinra 150 mg group, 291 ml/minute). The MRTs were 6.2 and 7.4 hours following administration of 50 mg of anakinra and 150 mg of anakinra, respectively. The terminal half-life of anakinra in serum was ~4 hours (3.8 hours for anakinra 50 mg and 4.7 hours for anakinra 150 mg).

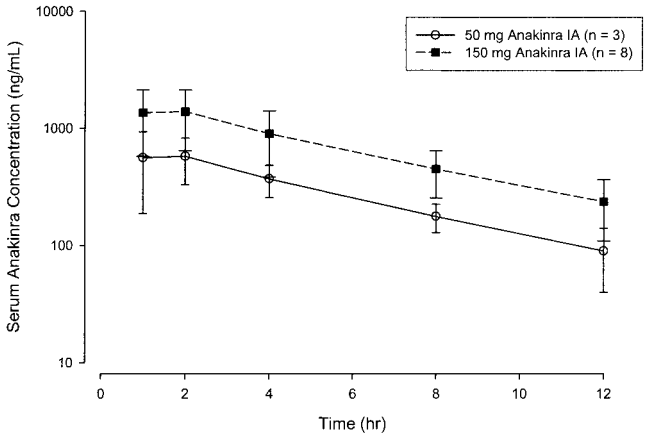

Figure 3. Mean ± SD anakinra concentration-time profile. Mean serum anakinra concentrations (ng/ml) following a single intraarticular (IA) injection of 50 mg or 150 mg anakinra through 12 hours postdose.

Safety. The percentage of patients reporting AEs was similar between the placebo group (59%) and the anakinra 150 mg group (60%) and slightly lower for the anakinra 50 mg group (38%) (Table 4). The most common AE was arthralgia (10%), with similar rates between the anakinra 150 mg group (12%) and the placebo group (12%) but a lower rate for the anakinra 50 mg group (3%). Headache (10% versus 1%), upper respiratory tract infection (8% versus 1%), back pain (8% versus 3%), and extremity pain (6% versus 0%) occurred more often in the anakinra 150 mg group than in the placebo group. AE occurrences related directly to the index knee were infrequent. Three patients reported joint effusion (1 in each treatment group), 2 patients reported burning sensations (1 each in the anakinra 150 mg group and the placebo group), 1 patient reported arthritis with effusion and redness (anakinra 150 mg group), and 1 patient reported hypoesthesia/

Table 4. Summary of adverse events (AEs)*

	Placebo (n = 69)	Anakinra 50 mg (n = 34)	Anakinra 150 mg (n = 67)	Total (n = 170)
All AEs	41 (59)	13 (38)	40 (60)	94 (55)
Leading to study withdrawal	0 (0)	0 (0)	0 (0)	0 (0)
Injection site reaction	4 (6)	2 (6)	2 (3)	8 (5)
Serious AEs	1 (1)	0 (0)	1 (2)	2 (1)
Infections	4 (6)	1 (3)	12 (18)	17 (10)
Leading to study withdrawal	0 (0)	0 (0)	0 (0)	0 (0)
Resulting in hospitalization	0 (0)	0 (0)	0 (0)	0 (0)
Serious infections	0 (0)	0 (0)	0 (0)	0 (0)
Death	0 (0)	0 (0)	0 (0)	0 (0)

* Values are the number (percentage) of subjects reporting at least 1 occurrence of an AE.

paresthesia (anakinra 150 mg group). All events were of mild or moderate intensity.

Four serious AEs were reported in 2 patients, none of which were determined by the investigators to be related to the study drug. One of these patients (in the placebo group) experienced a single serious AE of noncritical coronary artery stenosis. The other 3 serious AEs reported by a second patient (in the anakinra 150 mg group) included intense menstrual bleeding, altered mental status, noncardiac chest pain, and extremity pain. No deaths were reported.

Infections were reported in 10% of patients, more frequently for the anakinra 150 mg group (18%) compared with the anakinra 50 mg (3%) or the placebo group (6%) (Table 4). The only infections occurring more frequently for anakinra than for placebo, and occurring in more than 1 patient, were upper respiratory tract infections (6% versus 1%) and urinary tract infections (3% versus 1%). Infections were mild or moderate in all except 1 case (an incident of severe diarrhea). No serious infections or joint or bone infections were reported.

No clinically significant changes were observed for laboratory values, blood pressure, heart rate, respiratory rate, or temperature. Nine patients experienced at least 1 severe or life-threatening (National Cancer Institute Common Toxicity Criteria grade $\geq$3) change in laboratory measures. Four patients receiving placebo experienced 5 events, including 2 increases in the potassium level, 1 decrease in the potassium level, 1 decrease in the sodium level, and 1 increase in the calcium level. Five patients receiving anakinra experienced 5 events, including 2 increases in the glucose level, 2 decreases in the sodium level, and 1 decrease in the potassium level. None of these increases or decreases was clinically relevant in relation to adverse events.

DISCUSSION

In patients with knee OA treated with 50 mg or 150 mg of anakinra, the change score from baseline to week 4 in the WOMAC index showed no significant difference versus placebo. The response to placebo was relatively high (57% of OMERACT-OARSI responders at week 4), consistent with results of trials conducted in OA (23–25) using intraarticular injections (26,27).

Assessment of the WOMAC index at time points other than week 4 showed some indication of a short-term clinical effect of anakinra. The clinical response observed with anakinra on day 4 was greater than that observed with placebo, and the comparison between the anakinra 150 mg group and the placebo group approached statistical significance for the WOMAC pain subscore. This observation suggests that anakinra, with its short plasma half-life, may be effective at relieving OA symptoms at time points earlier than those examined in this study. Therefore, evaluating a more potent IL-1 inhibitor with a longer duration could provide greater understanding of the effect IL-1 inhibition might have on the relief of OA symptoms.

No significant improvement in clinical assessments was noted with either dose of anakinra, but the improvement in pain on day 4 was greater in magnitude for the 150-mg dose versus the 50-mg dose, although this was not observed as a clear trend across time points. Because this study was powered to compare anakinra 150 mg and placebo, the primary assessment of this study, fewer patients were randomized into the 50-mg group.

All of the secondary efficacy end points failed to show significant differences in change from baseline between anakinra and placebo. Moreover, no significant differences were noted between treatments in the biomarker evaluations of cartilage degradation, which were not performed until week 4.

The lack of significant effect of anakinra on OA of the knee in this clinical trial is in contrast with preclinical results (16–18). It is always difficult to translate the results observed in animals to the possible effects in humans. There were important differences in IL-1Ra administration in the preclinical versus clinical studies: repeated intraarticular administration or gene therapy (that may allow longer duration of protein delivery) in the preclinical setting, and a single intraarticular administration in the clinical setting. Furthermore, the preclinical studies did not address the analgesic response in animals but were performed to determine if IL-1Ra can protect the cartilage.

In the small cohort of patients with serum pharmacokinetics sampling, the maximum serum anakinra concentra-

tion occurred ~2 hours after intraarticular injection for both doses. The terminal serum half-life was ~4 hours, similar to the half-life after a single subcutaneous dose (28). In addition, the serum anakinra concentrations were below the quantification limit 24 hours postdose for all patients. These results suggest that there is no depot effect from intraarticular injection of anakinra. Repeated injections might be needed to obtain and sustain any modest reduction in pain. Since anakinra appeared to be distributed systemically, or outside the joint, after intraarticular injection, this may also explain the lack of a significant effect on knee symptoms, which would assume a more localized IL-1 inhibition.

Repeated dosing could help determine whether there is an augmented effect or tachyphylaxis with additional injections. Indeed, in experimental models of OA, a decrease in the severity of histologic lesions of cartilage was only observed after repeated intraarticular injections or following local delivery of IL-1Ra by gene transfer (16,17). In vitro experiments suggest that to block IL-1β activity in cartilage, an excess of 10–100-fold the amount of IL-1Ra is necessary. IL-1 levels in synovial fluid from patients with OA are extremely low (<1.0 pg/ml to <100.0 pg/ml), if present at all (29). In this study, anakinra was hypothesized to counter symptoms of pain and stiffness or changes in cartilage metabolism that may be related to excess IL-1 or an IL-1–related effect. IL-1Ra may be up-regulated in OA and rheumatoid arthritis and therefore result in an increased IL-1Ra:IL-1 ratio in the synovial fluid of some patients, requiring much more IL-1Ra than was provided in the 150-mg dose (30). A higher dose or repeated dosing may also have demonstrated a more pronounced difference. However, the 150-mg dose was chosen as the highest known tolerable amount to administer in this population (19).

As was observed in the pilot trial (19), postinjection knee effusion was infrequent in this study and was observed equally with placebo and anakinra. No patients experienced septic arthritis (joint infection).

In summary, anakinra at a dose of 50 mg or 150 mg was well tolerated as a single intraarticular injection in patients with OA of the knee. However, no improvements in knee pain, function, stiffness, or cartilage turnover were observed in patients treated with anakinra compared with placebo, although a tendency toward pain reduction with anakinra 150 mg versus placebo was noted on day 4. Despite the lack of a significant clinical benefit of anakinra, some of the study results suggest that IL-1 inhibition may be therapeutically important in OA of the knee. Further studies with longer acting and more potent IL-1 antagonists may better elucidate and explore this potential.

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AUTHOR CONTRIBUTIONS

Dr. Chevalier had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Chevalier, Goupille, Burch, Appleton.

Acquisition of data. Goupille, Beaulieu, Burch, Conrozier, Loeuille, Kivitz, Silver.

Analysis and interpretation of data. Chevalier, Goupille, Bensen, Appleton.

Manuscript preparation. Chevalier, Goupille, Burch, Bensen, Conrozier, Loeuille, Silver, Appleton, Marc D. Kubasak (nonauthor, Amgen, Inc.).

Statistical analysis. Lifen Zhou (nonauthor, Amgen, Inc.).

ROLE OF THE STUDY SPONSOR

Amgen, Inc. sponsored the clinical trial and retains the data although all authors had full access to the data. Amgen contributed to the study design, statistical analysis, data interpretation, and manuscript preparation. Amgen agreed to submit the manuscript for publication and approved the content of the submitted manuscript.

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