Safety Study of Intraarticular Injection of Interleukin 1 Receptor Antagonist in Patients with Painful Knee Osteoarthritis: A Multicenter Study

XAVIER CHEVALIER, BRUNO GIRAUDEAU, THIERRY CONROZIER, JOCELYNE MARLIERE, PHILIPPE KIEFER, and PHILIPPE GOUPILLE

ABSTRACT. ***Objective.*** Interleukin 1 (IL-1) plays a pivotal role in the pathogenesis of osteoarthritis (OA). In animal models of OA, IL-1 blockade by IL-1 receptor antagonist (IL-1Ra) can slow the progression of disease. We examined the safety of intraarticular (IA) injections of recombinant human IL-1Ra in patients with knee OA.

Methods. A prospective multicenter trial was conducted using the continual reassessment method. Six doses were considered, 0.05 mg up to 150 mg IL-1Ra, and the trial was double-blind regarding the dose administered. Patients with symptomatic knee OA and without synovial fluid effusion were included. Acute inflammatory reaction (the primary endpoint defining intolerance) was recorded if pain increase over 30 mm on 100 mm visual analog scale and synovial fluid effusion occurred within 72 h after the IA injection. As a secondary aim, efficacy was estimated (by total pain and Western Ontario and McMaster University OA functional index) until Month 3.

Results. One patient received 0.05 mg and 13 patients received 150 mg of IL-1Ra. No acute reaction occurred (one patient experienced postinjection joint swelling with no pain) and the 150 mg dose was considered the maximum tolerated dose (intolerance level 0%; confidence interval 0, 9.1%). A significant improvement was still observed until Month 3 in the 13 patients who received 150 mg IL-1Ra: pain improved by –20.4 ± 23.3 mm (p = 0.008) and WOMAC global score by –19.5 ± 20.1 (p = 0.005).

Conclusion. IA injection of IL-1Ra in patients with knee OA was well tolerated and did not induce any acute inflammatory reaction. The feasibility of such IA injections of IL-1Ra opens a promising therapeutic perspective for patients with OA. (J Rheumatol 2005;32:1317–23)

Key Indexing Terms:
OSTEOARTHRITIS
INTERLEUKIN 1ß
INTERLEUKIN 1ß ANTAGONIST
INTRAARTICULAR

Symptomatic osteoarthritis (OA) of the knee affects millions of people, its prevalence increasing with age: 7% at age 65–70 years up to 11.2% after age 80[1]. Current treatments limit pain and improve function[2]. Since it seems that the clinical evolution may be linked to the progression of the disease, there is a need for a novel treatment of OA that combines prevention of cartilage destruction and analgesic effect[3].

OA is marked by a degradation of the cartilage extracellular matrix, resulting from an imbalance between catabolic and anabolic functions of chondrocytes, mediated by proinflammatory cytokines[4]. Among them, interleukin 1ß (IL-1ß) is produced in paracrine and autocrine fashion, leading to strong expression and activation of proteolytic enzymes (which degrade the collagen and proteoglycan network) and inhibition of the synthesis of collagen type 2 and proteoglycans[5-9]. Animal models of OA support the dominant role of IL-1ß early in the disease process[10]. Thus, inhibition of IL-1ß may be an important strategy for decreasing the cartilage matrix degradation. IL-1ß activity can be blocked physiologically by a receptor antagonist (IL-1Ra) and by non-signal soluble receptor II[11]. IL-1Ra is an endogenous, competitive antagonist of the IL-1 type I receptor (with low affinity for type II receptor), which modulates the biological

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actions of IL-1 (such as production of enzymes) by prevention of signal transduction[11]. IL-1Ra gene deficient mice developed a rheumatoid-like disease, indicating the key role of IL-1Ra in controlling IL-1ß activity[12]. In OA, deficient expression by chondrocytes of innate regulators such as IL-1Ra may allow the catabolic effects of IL-1 to proceed unopposed[13]. Studies in different animal models of OA using intraarticular (IA) delivery of IL-1Ra have shown its capacity to slow the progression of cartilage lesions[14-17].

A recombinant form of human IL-1Ra, anakinra [recombinant methionyl human receptor antagonist (r-met HuIL-1Ra)], is a competitive antagonist of IL-1 that blocks the action of IL-1 with no detection of agonist activity. In controlled clinical trials in patients with rheumatoid arthritis (RA), anakinra in daily subcutaneous administration provided significant symptomatic improvement and slowed the radiographic progression[18]. In OA, it seems more appropriate to deliver IL-1Ra by an IA route to reach the cartilage lesions.

We undertook a randomized trial of IA injection of IL-1Ra in patients with knee OA; our primary aim was to characterize the safety profile of such administration. The secondary objective was to determine the 3-month efficacy effect of IL-1Ra on pain and function.

MATERIALS AND METHODS

Patients. The study was carried out on patients aged 18 years or older, fulfilling the American College of Rheumatology criteria for knee OA (in case of bilateral symptomatic involvement, only the more painful joint was considered), with a pain level > 30 mm and < 70 mm on a 100 mm visual analog scale (VAS), who had no significant synovial effusion. Radiographic evidence of tibiofemoral (medial or lateral) OA (within the last 12 mo) was required, whatever the radiological stage. Stable doses for at least 2 months were required for patients already using slow-acting drugs (such as chondroitin sulfate, avocado and soya extracts, diacerhein, glucosamine sulfate) and at least 3 days for patients taking nonsteroidal antiinflammatory drugs (NSAID). The following exclusion criteria were retained: severe illness, cancer within the previous 5 years except basal cell carcinoma or *in situ* cancer (uterus or thyroid), history of recurrent or chronic infection or current acute infection, uncontrolled diabetes, cardiovascular diseases requiring antivitamin K treatments or longterm treatment with aspirin (> 1 g/day), leukopenia < 2.0 x 10^9/l, thrombocytopenia < 100 x 10^9/l, positive test for human immunodeficiency, hepatitis B or hepatitis C virus, pregnant or breast-feeding women, inadequate contraception, psychiatric disorders, secondary OA, isolated femoropatellar OA, local or systemic contraindication to steroid, allergy to *Escherichia coli* derivatives, or receipt of IA steroid injection within 1 month and/or hyaluronic acid within 3 months prior to the study.

Three French academic rheumatology units were involved in this clinical trial (Tours, Lyon-Sud, and Creteil).

The study protocol was approved by the Comité Consultatif de Protection des Personnes se prêtant à la Recherche Biomédicale of Tours, and patients' written informed consent was obtained. The study was conducted in accord with the Declaration of Helsinki.

Study design. Tolerance of IA injections was studied by assessing the dose-intolerance relationship. This phase II study was planned using a sequential Bayesian method to assess the maximum tolerated dose (MTD) and it was double-blind regarding the dose administered[19]. The target tolerance level, defining the maximum acceptable intolerance, was fixed at 5% [by analogy with the acute inflammatory reaction observed with IA injections of hyaluronic acid]. A set of 6 dose levels was selected (0.05, 5, 10, 50, 100, and 150 mg) and each was associated to an *a priori* intolerance level (respectively fixed at 0.1, 1, 3, 5, 10, and 20%). In the absence of previous study with IA injection in humans, doses were selected empirically to give a range that was considered to start from a "no effect" dose (0.05 mg) to the maximum dose studied in pivotal RA clinical trials using the subcutaneous route (150 mg)[18]. The remaining doses were chosen to be equally distributed within this range, taking into account constraints due to the drug presentation (vials of 40 mg/ml and 200 mg/ml). The first patient was planned to receive the lowest dose. Then, any time the safety endpoint (day 4) was assessed for one patient, the 6 intolerance levels were *a posteriori* reestimated, and the next patient was planned to receive the dose level closest to the 5% intolerance target level.

Study drug. Anakinra (Amgen, Thousand Oaks, CA, USA) was supplied in vials in sterile solution (stored at +2°C) of either 40 mg/ml or 200 mg/ml. For each patient the dose was reconstituted under sterile conditions to achieve concentration from 0.05 mg up to 150 mg in 1.5 ml.

All treatments were administered by a senior rheumatologist using the external lateral patellar route under aseptic conditions.

Concomitant therapy. Changes in NSAID or analgesic intake were not allowed until Day 4 (3 days after injection), but were allowed thereafter during the course of the study if they were clinically indicated. Analgesics were stopped at least 12 h before regular visits.

All types of IA injections including corticosteroids, hyaluronic acid, and systemic administration of corticosteroids and stage 3 analgesics (morphine) were prohibited during the study.

Outcome measures

Safety endpoint. Local safety. The primary endpoint outcome was local tolerance. An acute inflammatory reaction, characterized by a 30 mm increase of pain (on a 100 mm VAS) associated with a synovial fluid effusion within the 3 days following the IA injection, was considered a manifestation of intolerance.

General safety. Clinical side effects were recorded. Determination of serum white cell count, platelet count, hemoglobin, and liver enzymes (ALAT and ASAT) was performed at entry and 3 days after the injection.

Efficacy endpoints. Efficacy was estimated from VAS measuring total pain and the Western Ontario and McMaster University OA algofunctional index (WOMAC) in the 3 domains. Patients with more than 50% improvement of pain intensity compared with baseline level were considered responders. Pain was determined at entry on the day of injection (Day 1) and then on Day 2, 3, 4, 11, 30, and 90. WOMAC algofunctional index was recorded on Day 1, and then along with the patient global assessment of treatment efficacy on Day 4, 11, 30, and 90 after the IA injection.

Consumption of analgesics and NSAID was recorded in a patient diary.

Blinding. Except for the first included patient (physicians knew that he was planned to receive the lowest dose), both patients and physicians were blinded to the dose.

Number of patients. We planned that a maximum of 25 subjects could be enrolled into the trial, which has been shown to allow the MTD to be determined, provided it is included in the range of tested doses[20]. Moreover, we planned to apply stopping rules as defined by Zohar and Chevret[21], which may lead to premature termination of the trial in case (1) all doses are unacceptably untolerated or (2) all doses are well tolerated or (3) because the currently administered dose is expected to be the MTD.

Statistical analysis. Primary analysis. A logistic model was chosen to assess the dose-response relationship. Thus, defining $Prob_i$ as the intolerance level associated to dose i (d_i) we have:

$$Prob_i \quad \frac{\exp(2+\theta \cdot d_i)}{1+\exp(2+\theta \cdot d_i)} \quad i = 1, \Lambda, 6$$

The constant 2 was determined from a calibration step of the model in view of its operational properties when considering the set of selected doses and

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the *a priori* fixed intolerance levels. Theta was assumed to be exponentially distributed with an *a priori* mean fixed at 0.5 (value fixed from the calibration step), which enabled the large initial uncertainties about the hypothesized dose-intolerance relationship to be incorporated. Any time a safety outcome was observed, this result was combined with the prior information by applying the Bayes theorem in order to update the mean distribution of theta, and thus the dose-response distribution. The next allocation was then based on these updated (posterior) intolerance levels as if they were the prior, and the process was iterated. Analyses were performed using the Bayesian Phase I or II Clinical Trials (BPCT) software developed by Zohar, *et al*[22].

Secondary analysis. Statistical analysis of efficacy outcome was conducted within each subgroup of patients defined by the dose administered. For quantitative data, mean and standard deviation were provided. Evolution of efficacy parameters (pain, WOMAC) was evaluated by Wilcoxon signed-rank test for each assessment compared to baseline.

RESULTS

Assigned doses. The first patient received the 0.05 mg dose. Since no acute inflammatory reaction was observed, the *a posteriori* intolerance level of the 150 mg dose was estimated at 0.4%, leading to administration of a 150 mg dose to the second patient. Then, since we observed no acute reaction, any subsequent patient received the 150 mg dose.

Patients. Fourteen patients were included in the study (epidemiological data are summarized in Table 1). Since we observed no adverse reaction, the study could have been stopped earlier. However, we decided to proceed, to achieve a better estimate of secondary outcomes. Approval from the ethics committee was obtained before additional exposure.

Safety data. Local safety. No episode of acute reaction was observed. No patient experienced increased pain following the IA injection. One patient had a synovial fluid effusion (sterile fluid with 150 cells/mm^3) within 3 days after IA injection but with no increase of pain. This episode was considered by the investigator as not related to study drug, and synovial fluid effusion did not recur. Otherwise, we observed no episode of synovial fluid effusion in other patients during the followup. No cutaneous injection site reactions were observed.

Thus for the empirically predefined doses, 150 mg IL-1Ra was well tolerated and was considered the MTD in this study. The *a posteriori* intolerance level associated with this 150 mg dose was thus estimated at 0% (with 95% CI of 0–9.1%).

General safety. One patient developed a colorectal cancer unrelated to the IL-1Ra injection (symptoms were present before injection of IL-1Ra). No blood test abnormalities were observed.

Efficacy data. Results are summarized in Figures 1A, 1B. Results for each patient are shown in Figure 2 and Table 2.

Level of pain on VAS. Mean decrease in the absolute change in the level of pain was quite stable throughout the study, varying from –19.2 ± 21.8 mm at Day 2 to –20.4 ± 23.3 mm at Month 3 in the 150 mg group (n = 13; Figure 1A). The relative decrease of pain level was statistically significant

Table 1. Patient characteristics at baseline.

	Total, n = 14	Dose 0.05 mg, n = 1	Dose 150 mg, n = 13
Age, yrs, mean ± SD	70 ± 5	72	70 ± 6
Male sex, n (%)	6 (42.9)	1	5 (38.5)
BMI, kg/m^2, mean ± SD	26.9 ± 2.7	27.7	26.8 ± 2.8
Duration of OA, yrs, median (range)	9 (0.3, 19)	14	8 (0.3, 19)
Pain, 100 mm VAS, mean ± SD	50.5 ± 12.2	65	49.4 ± 11.9
WOMAC, (Mean ± SD)	44 ± 13.3	55.6	43.1 ± 13.4
Medial knee OA, n (%)	12 (85.7)	0	12 (92.3)
Lateral knee OA, n (%)	4 (28.6)	1	3 (23.1)
Femoropatellar involvement	8 (57.1)	1	7 (53.8)
Contralateral knee involvement	9 (64.3)	1	8 (61.5)
Hip OA	3 (21.4)	1	2 (15.4)
Hand OA	4 (28.6)	0	4 (30.8)
Treatments			
Analgesics (acetaminophen and/or acetaminophen plus codeine), n (%)	14 (100.0)	1	13 (100.0)
NSAID, n (%)	6 (42.8)	0	6 (46.2)
SYSADOA, n (%)	8 (57.1)	1	7 (53.8)
Kellgren-Lawrence radiographic stage (%)			
1	1 (7.1)		1 (7.7)
2	4 (28.6)		4 (30.8)
3	5 (35.7)	1	4 (30.8)
4	4 (28.6)		4 (30.8)

BMI: body mass index, VAS: visual analog scale, NSAID: nonsteroidal antiinflammatory drugs, SYSADOA: symptomatic slow-acting drugs in OA.

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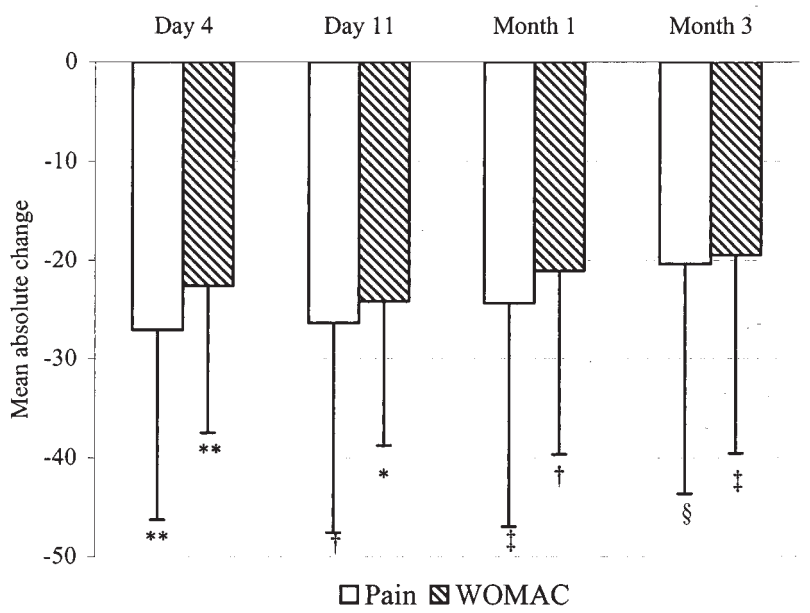

Figure 1A. Absolute change from baseline in pain VAS (mm) and WOMAC assessment; patients receiving 150 mg (n = 13). Solid lines represent standard deviation in reduction. *p < 0.001, **p = 0.001, †p = 0.002, ‡p = 0.005, §p = 0.008 compared with baseline.

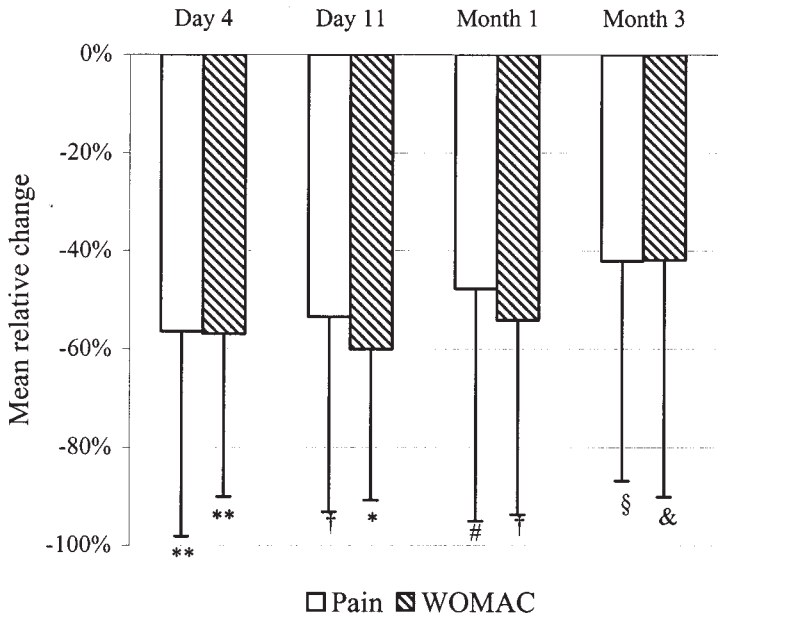

Figure 1B. Relative change from baseline in pain VAS (mm) and WOMAC assessment; patients receiving 150 mg (n = 13). Solid lines represent standard deviation in reduction. *p < 0.001, **p = 0.001, †p = 0.002, p = 0.006, §p = 0.008, &p = 0.011 compared with baseline.

until Month 3 (–42.1% ± 44.8% compared with baseline; p = 0.008; Figure 1B).

In the patient treated with 0.05 mg IL-1Ra, pain decreased at all points (except at Day 11) from –24 mm at Day 2 to –21 mm at Month 3.

WOMAC scores. Similar decreases in WOMAC global scores were observed in the 13 patients injected with the 150 mg dose, varying from –22.6 ± 14.9 mm at Day 4 (p = 0.001) to –19.5 ± 20.1 mm at Month 3 (p = 0.005; Figure 1A). The relative decrease in the WOMAC global score was

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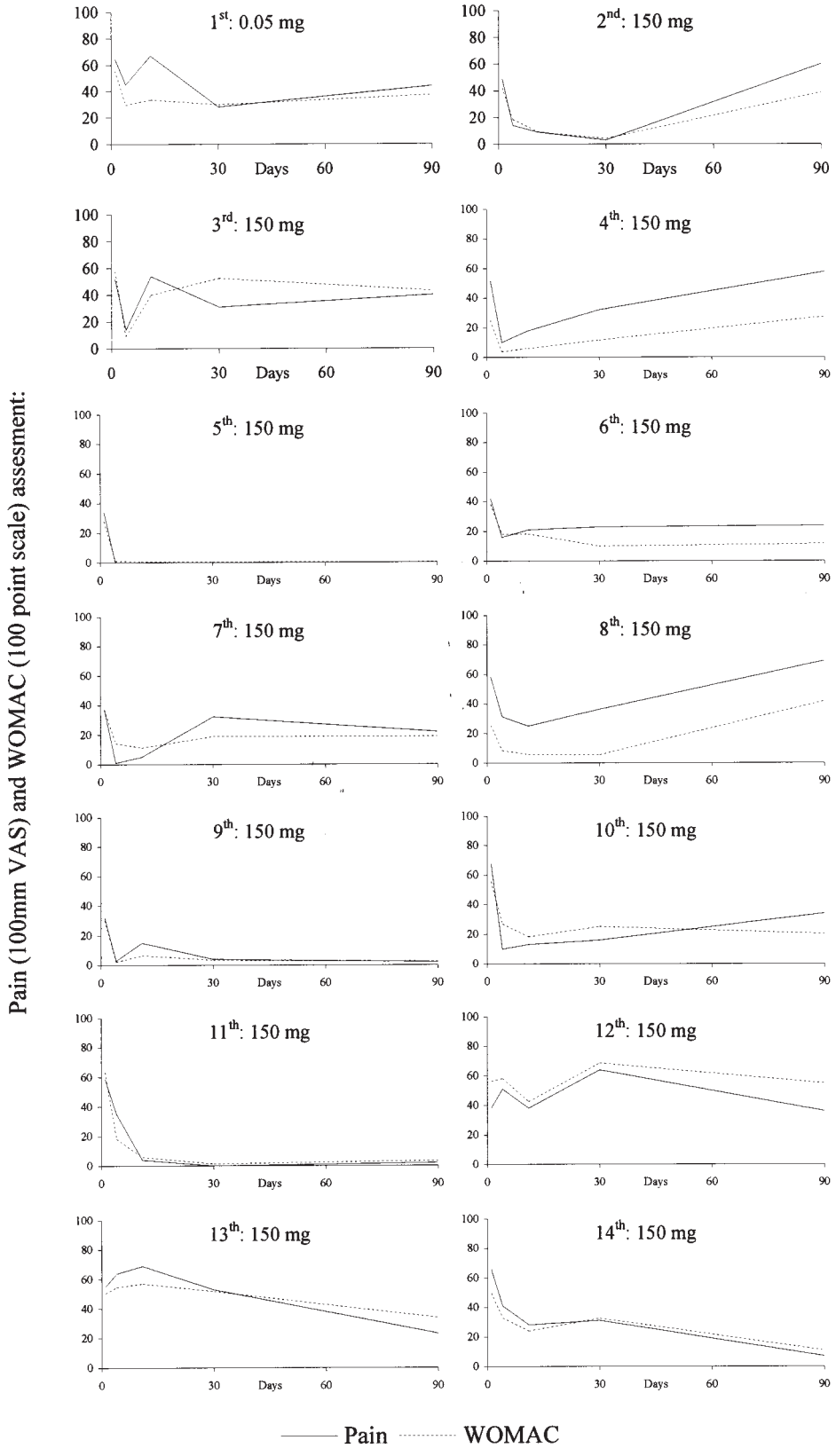

Figure 2. Patients 1 to 14: individual response profiles for pain and WOMAC scores.

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Table 2. Profile of responders, showing IL-1Ra dose, with respect to pain and WOMAC global score.

	1 0.05 mg	2 150 mg	3 150 mg	4 150 mg	5 150 mg	6 150 mg	7 150 mg	8 150 mg	9 150 mg	10 150 mg	11 150 mg	12 150 mg	13 150 mg	14 150 mg
VAS pain														
Month 1	R+	R+	–	–	R+	–	–	–	R+	R+	R+	–	–	R+
Month 3	–	–	–	–	R+	–	–	–	R+	R+	R+	–	R+	R+
WOMAC														
Month 1	–	R+	–	R+	R+	R+	R+	R+	R+	R+	R+	–	–	R+
Month 3	–	–	–	–	R+	R+	R+	–	R+	R+	R+	–	–	–

R+: response > 50% of improvement compared with baseline. "–": response < 50% of improvement compared with baseline.

statistically significant until Month 3 (–41.9% ± 48.3% compared with baseline; p = 0.011; Figure 1B). In the patient treated with 0.05 mg IL-1Ra, the WOMAC global score decreased at all points from –26.1 at Day 4 to –18.5 at Month 3.

Magnitude of response. Results are shown in Figure 2 and Table 2. At Month 3, 6 patients injected with 150 mg IL-1Ra were responders with respect to pain. All these patients were improved at Month 1, except in one case. Additionally, one patient (Patient 6) was very close to the definition of a responder: 43% reduction in pain score at Month 3. For WOMAC global score among the 6 patients considered responders at Month 3 according to their level of pain: 4 demonstrated the same response profile, one was considered a nonresponder, and the other responded only until Month 1. Additionally, 2 patients were considered responders at Month 3 with respect to WOMAC global score but not for pain, including the patient that was close to the responder definition with respect to pain level improvement. Finally, 10 patients were responders considering the response at Month 1 for WOMAC global score.

The patient injected with 0.05 mg IL-1Ra was considered a nonresponder at Month 3 with respect to pain and WOMAC global score.

Correlations with radiological and clinical data. There was no correlation between radiological stage or duration of disease and the clinical response profile.

Patient global assessment of treatment efficacy. A high level of patient satisfaction was achieved in the group of patients injected with 150 mg: on a 100 mm VAS, the patient global assessment of treatment efficacy ranged from 75.1 ± 20.4 at Day 4 to 70.5 ± 32.0 at Month 3, while it was only 41 at Day 4 to 31 at Month 3 for the patient injected with the low dose.

Consumption of analgesics and NSAID. In the group of 13 patients treated with 150 mg IL-1Ra, all were taking analgesics at baseline and only 7 continued analgesics at Month 3. Six patients were treated with NSAID at baseline and 4 continued at Month 3.

DISCUSSION

The main result of our study is that IA injection of 150 mg IL-1Ra is well tolerated in patients with painful knee OA. We defined intolerance (main endpoint) as an acute inflammatory reaction, characterized by a 30 mm increase of pain on a 100 mm VAS associated with a synovial fluid effusion within the 3 days following the IA injection. Such a local adverse event has been observed in 7% of patients after IA injection of hyaluronic acid in patients with knee OA[23].

Outside the occurrence of an acute inflammatory reaction, IA injection of IL-1Ra did not induce any increase in the level of pain. One patient presented a noninflammatory, asymptomatic synovial fluid effusion, which may be related to the spontaneous evolution of the disease. Otherwise, we observed no cutaneous local reaction (at the site of injection) or systemic side effects (including change in blood tests) following this single IA injection.

We chose an original method to determine the MTD (the continual reassessment method, which is a Bayesian scheme); compared with a more classical study with randomized parallel groups receiving different doses of the tested drug, this method can allow reducing the number of patients exposed to a possible "toxic" dose[20,21]. We chose this design to permit stopping the trial rapidly in case of intolerance. We empirically chose dose intervals from 0.05 mg up to 150 mg of IL-1Ra, far above the synovial fluid level of IL-1 in OA (varying from < 1.0 pg/ml to 20 pg/ml)[24,25]. One would expect to block IL-1 type I receptor with such a concentration. Because no acute reaction was observed in the second patient injected with 150 mg, only the maximum dose was tested further. The IA route rather than a systemic route was chosen to deliver IL-1Ra for the following reasons: (1) the cartilage is avascular, thus IA injection of IL-1Ra is more likely to reach the superficial cartilage lesions and to block IL-1 type I receptor on the cell surface; and (2) IA injection may preclude the systemic and local cutaneous side effects of systemic administration[18].

There is some evidence that IL-1ß is involved not only in the structural degenerative processes of OA but also plays an important role in the pathophysiology of OA pain. Osteoarthritic chondrocytes under IL-1ß stimulation produced a high level of prostaglandin E_2 (PGE_2), a well known pain mediator involved at peripheral and central neurological levels[26,27]. Thus, in an equine model of OA, IA

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gene transfer of IL-1Ra resulted in significant improvement in clinical indicators related to pain, together with structural improvement[17]. In a canine model of OA (section of anterior cruciate ligament), direct IA injections of IL-1Ra (up to 4 mg) diminished the development of osteophytes, reduced the extent of macroscopic cartilage lesions, and decreased the expression of collagenase 1[14].

Our study is the first performed in human subjects. Discussion of a potential analgesic effect of IL-1Ra is purely speculative in the absence of a control arm. Longterm benefit in the responders may suggest a therapeutic effect, although the study was not designed to answer to the question of efficacy. Further, it is well known that IA injection can be associated with a significant placebo effect (up to 80% of the effect of IA injections of hyaluronic acid might be due to a placebo effect)[28].

The only conclusion that can be drawn from our study is that single IA injection of IL-1Ra (up to 150 mg) in patients with knee OA was well tolerated and did not cause acute inflammatory reactions. This preliminary safety study constitutes a first step in the concept of IL-1 inhibition in OA. Only a randomized placebo controlled study can determine the efficacy of IA injection of IL-1Ra for knee OA.

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