EFFICACY OF SUSTAINED BLOOD LEVELS OF INTERLEUKIN-1 RECEPTOR ANTAGONIST IN ANIMAL MODELS OF ARTHRITIS

Comparison of Efficacy in Animal Models with Human Clinical Data

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Objective. To determine the role of interleukin-1 receptor antagonist (IL-1Ra) in rat adjuvant arthritis and rat type II collagen–induced arthritis, and to compare the efficacy in rat models with that seen in human clinical trials of IL-1Ra.

Methods. Rats with developing adjuvant arthritis or established collagen-induced arthritis were treated with IL-1Ra by continuous infusion in order to determine and maintain efficacious blood levels of this IL-1 inhibitory protein in the rats for comparison with human clinical data. The effects of treatment in the rats were monitored by sequential caliper measurement of the ankle joints, determination of final paw weights, and histologic evaluation with particular emphasis on bone and cartilage lesions. The effects of IL-1Ra on joint swelling and radiographic bone damage in patients with rheumatoid arthritis (RA) in a 6-month trial were compared with the findings in rats.

Results. Dramatic differences in the profile of IL-1Ra activity were seen between the 2 groups of rats. Modest antiinflammatory effects were observed in the adjuvant arthritis rats treated with IL-1Ra. However, marked inhibition of bone resorption occurred, even at doses with which antiinflammatory activity was not seen. In contrast, IL-1Ra treatment of rats with established collagen-induced arthritis resulted in nearly complete suppression of all aspects of the disease when adequate blood levels of IL-1Ra were maintained. Treatment of RA patients with IL-1Ra (150 mg daily) resulted in modest inhibition of joint swelling and inhibition of radiographic progression of bone lesions.

Conclusion. IL-1 appears to be of major importance in mediating the bone resorption that occurs in rat adjuvant arthritis, but is less important in the pathogenesis of periartricular inflammation in this disease. In contrast, IL-1 is of major importance in mediating all aspects of disease progression in rat collagen-induced arthritis. Similar to the response in adjuvant arthritic rats, RA patients treated with IL-1Ra showed only modest antiinflammatory activity, but had evidence of inhibition of progression of bone resorption. However, a comparison of the plasma levels of IL-1Ra in humans and rats suggests that the optimal level of dosing for continuous saturation of IL-1 receptors may not have been achieved in humans, although this was achieved in the rat studies.

Rheumatoid arthritis (RA) is a chronic disease that is characterized by inflammation of the joints and concomitant destruction of cartilage and bone. The involvement of cytokines, particularly interleukin-1 (IL-1) and tumor necrosis factor α, in the pathogenesis of RA is now well accepted. As a result of numerous studies in animal models as well as in patients with the disease (1–4). The IL-1 receptor antagonist (IL-1Ra) is a specific receptor antagonist that competitively inhibits binding of IL-1α and IL-1β to human and animal types I and II IL-1 receptors (5). Several clinical trials have been completed in which IL-1Ra has been administered long term to patients with RA (6). Results indicate that treatment of RA patients with IL-1Ra lowers the level of
acute-phase proteins and swollen joint counts and may inhibit radiographic disease progression (7).

Preclinical data on IL-1 inhibition in various mouse models of arthritis indicate that results have been variable depending on the model and dosing regimen used. Data from rat models of arthritis have primarily been generated in the reactivated streptococcal cell wall–induced arthritis model, in which results have been either positive or negative depending on the timing of dosing (8).

Rat adjuvant arthritis is an experimental model of polyarthritis that has been widely used for preclinical or clinical testing of numerous antiarthritic therapeutic agents (9–11). The hallmarks of this model are reliable onset of robust polyarticular inflammation, marked bone resorption, and periosteal bone proliferation. Cartilage destruction occurs, but is disproportionately mild in comparison with the inflammation and bone destruction that occur.

Rat type II collagen–induced arthritis is produced when rats are immunized against homologous or heterologous type II collagen. The resulting polyarthritis is characterized by marked cartilage destruction that is associated with immune complex deposition on articular surfaces, bone resorption and periosteal proliferation, and moderate-to-marked synovitis and periarticular inflammation. The lesions in type II collagen–induced arthritis are somewhat more analogous to those seen in human RA (12,13). However, adjuvant arthritis has been used much more extensively for pharmaceutical testing, and therefore more data from this model exist for comparison with humans.

In the present study, we determined the importance of IL-1 in the pathology and pathogenesis of arthritis in these 2 different rat models. In addition, we correlated plasma levels of IL-1Ra with the inhibitory effects that were seen. This was done using continuous intravenous (IV) or subcutaneous (SC) infusion in tethered animals in order to maintain consistent blood levels, despite the relatively rapid clearance (as compared with that in humans) of this protein. Since the binding of IL-1Ra to the rat type I receptor is similar to that of the human type I receptor (Bendele A: unpublished data), we hypothesized that maintenance of similar plasma levels should result in some biologic effect in both rats and humans, and that the effect would be determined by the relative importance of IL-1 in the pathogenesis of the arthritis in the animal models and in the human disease.

IL-1Ra was tested in established rat type II collagen–induced arthritis, a model in which arthritis is present at the time of initiation of dosing. IL-1Ra was also evaluated in developing adjuvant arthritis, a model in which treatment is initiated prior to the onset of arthritis. The data obtained from the rats (plasma levels and efficacy in both models) were then compared with the efficacy (7) and plasma levels of IL-1Ra in humans for the purpose of determining which model was more predictive of the observed activity of IL-1Ra in patients with RA, and to provide support to the hypothesis that optimizing the delivery of IL-1Ra to maintain more consistent blood levels might improve its efficacy in humans.

**MATERIALS AND METHODS**

**Animals.** Female and male Lewis rats (200–250 gm; Charles River, Portage, MI) were used in these studies. Animals were allowed to acclimate for at least 3 days prior to initiation of experimentation. Rats were housed 1 per cage in plexiglass infusion cages with wire bottoms and were allowed ad libitum access to food and water. All animal use was in accordance with the US Department of Agriculture guidelines for humane care.

**Materials.** Recombinant IL-1Ra and its vehicle were produced at Amgen (Boulder, CO). Infusion materials included Velcro jackets and backpacks (fabricated at Amgen), polyethylene-50 (PE-50) tubing, and infusion swivels (Life Sciences Instruments, Woodland Hills, CA). Infusion pumps were from Harvard Apparatus (South Natick, MA). Freund’s complete adjuvant (CFA) and Freund’s incomplete adjuvant (IFA) were obtained from Sigma (St. Louis, MO) and Difco (Detroit, MI), respectively. The synthetic adjuvant N,N-dioctadecyl-N’,N’-bis(2-hydroxyethyl) propanediamine (lipodilamine; LA) was from BolderPath (Nederland, CO). Type II collagen was purchased from Elastin Products (Owensville, MO) and endotoxin (lipopolysaccharide type L-3129) was from Sigma.

**Preparation for continuous IV or SC infusion.** Rats were acclimated to wearing Velcro jackets for 3–4 days prior to implantation of the PE-50 cannulas in the jugular vein or subcutis of the dorsal back. Prior to cannula implantation, the hair over the dorsum was clipped and the skin scrubbed with Betadine and alcohol. An incision was made between the scapulae with a #11 blade, and ~7 inches of PE-50 tubing was inserted to the level of the lumbar vertebrae for SC cannulation. Cannulas were exteriorized between the scapulae, threaded up through the backpack, and ultimately connected to the line exiting the swivel apparatus via a 22-gauge half-inch connector. Rats that received IV cannulation had PE-50 tubing fused to sialastic jugular cannulas that were implanted in the jugular vein and then exteriorized between the scapulae.

Following surgery, rats were allowed to recover for at least 4 days prior to initiation of the adjuvant or collagen injections. For the collagen-induced arthritis studies, cannulated rats were hooked to infusion pumps on the day that they developed arthritis and entered the study. Adjuvant arthritis rats began receiving infusions on day 8 after the injection of adjuvant. Infusion solutions of IL-1Ra or vehicle were prepared so that the appropriate concentration was delivered at a flow rate of 100 µl/hour.
Collagen induction of arthritis. Female rats (8 per group) were given intradermal/SC injections of bovine type II collagen (2 mg/ml in IFA) at the base of the tail and in 3 sites over the back (250 μl in divided doses) on day 0 and day 7. On day 12, they were given an intraperitoneal injection of endotoxin (3 mg/kg). Onset of arthritis occurred over the next 5 days. As rats developed the disease, they were randomized to study groups, and treatment was initiated on the first day that clinical signs of arthritis were clearly visible.

Adjuvant induction of arthritis. Male rats (7 per group) were given single SC injections of 100 μl of CFA to which 5 mg/ml of LA was added. Treatments were initiated on day 8, which was 1–2 days prior to the onset of arthritis. As rats developed the disease, they were randomized to study groups, and treatment was initiated on the first day that clinical signs of arthritis were clearly visible.

Clinical assessment of collagen-induced arthritis. Caliper measurements of ankle joint width were done prior to the onset of arthritis, on the day of randomization, and on each subsequent study day until termination of the study on arthritis day 7. At termination, the tibiotarsal joint was transected at the level of the medial and lateral malleolus for determination of paw weights as another measure of inflammation. Paws were then collected in formalin for histopathologic evaluation.

Clinical assessment of adjuvant-induced arthritis. Caliper measurements of ankle joint width were done prior to the onset of arthritis and then every other day until the study was terminated on day 15 after injection of the adjuvant. At termination, the tibiotarsal joint was transected at the level of the medial and lateral malleolus for determination of paw weights as another measure of inflammation. Paws were then collected in formalin for histopathologic evaluation.

Histopathologic assessment. Ankle joints were stored in 10% neutral buffered formalin for at least 24 hours prior to placement in a Surgipath (Grayslake, IL) decalcifer. After ~1 week of decalcification, the digits were trimmed and the ankle joint was transected in the longitudinal plane to give approximately equal halves. These were processed for paraffin embedding, sectioned, and stained with hematoxylin and eosin for

Figure 1. Effects of interleukin-1 receptor antagonist (IL-1ra) in type II collagen–induced arthritis rats treated subcutaneously (SC) by continuous infusion. Samples (n = 8/group) were obtained after 7 days of infusion. Serum levels of IL-1ra (A) and final paw weights (B) in collagen-induced arthritis rats treated SC with vehicle or IL-1ra were determined (values on bars are the percentage inhibition compared with arthritic control rats; * = P ≤ 0.05, by 2-tailed t-test). Ankle joint diameter over time (C) was also measured in collagen-induced arthritis rats treated with vehicle or IL-1ra. Expression of the data as the area under the curve (D) demonstrates the percentage inhibition (values on bars) compared with arthritic control rats (* = P ≤ 0.05, by 2-tailed t-test).
general evaluation or with toluidine blue for specific evaluation of cartilage changes. Multiple sections were prepared to ensure that the distal tibia with both cortices was present and that abundant distal tibial medullary space was available for evaluation.

Ankles of adjuvant arthritic rats were given scores of 0–5 for bone resorption, according to the following criteria: 0 = normal; 1 = minimal (small areas of resorption, not readily apparent on low magnification, in the distal tibial trabecular or cortical bone; rare osteoclasts); 2 = mild (more numerous areas of resorption, not readily apparent on low magnification, in the distal tibial trabecular or cortical bone; more numerous osteoclasts); 3 = moderate (obvious resorption of the medullary trabecular and cortical bone, without full-thickness defects in the cortex; loss of some medullary trabeculae; lesion apparent on low magnification; more numerous osteoclasts; no resorption in the smaller tarsal bones); and 4 = marked (full-thickness defects in the cortical bone, often with distortion of the profile of the remaining cortical surface; marked loss of the medullary bone of the distal tibia; numerous osteoclasts; resorption also present in the smaller tarsal bones).

In addition to subjective scoring of bone resorption, numbers of clearly discernable osteoclasts in 5 fields (at 40× magnification) in areas of active bone resorption (if present) in the distal tibia were counted. The mean number of osteoclasts for each joint was determined.

Ankles of adjuvant arthritic rats were also scored 0–5 for inflammation, according to the following criteria: 0 = normal; 1 = minimal infiltration of inflammatory cells in periarticular tissue; 2 = mild infiltration, with moderate edema; 3 = moderate infiltration, with moderate edema; and 5 = severe infiltration, with severe edema. Cartilage damage was not scored in the adjuvant arthritis model because we have generally found this to be a minor feature and therefore not reliable for evaluation of potential treatment effects.

Histopathologic scoring of the tibiotarsal joints of rats with collagen-induced arthritis was similar to that for inflammation and bone resorption in the adjuvant arthritic rats. In addition, cartilage damage and pannus scores (range 0–5) were included because of the nature of the pathology in the collagen-induced arthritis model. Cartilage damage was scored according to the following criteria: 0 = normal; 1 = minimal (minimal-to-mild loss of cartilage evident on toluidine blue staining, with no obvious chondrocyte loss or collagen disruption); 2 = mild (mild loss of cartilage on toluidine blue staining, with mild focal [superficial] chondrocyte loss and/or collagen disruption); 3 = moderate (moderate loss of cartilage on toluidine blue staining, with moderate multifocal [depth to middle zone] chondrocyte loss and/or collagen disruption); 4 = marked (marked loss of cartilage on toluidine blue staining, with marked multifocal [depth to deep zone] chondrocyte loss and/or collagen disruption); and 5 = severe (severe diffuse loss of cartilage on toluidine blue staining, with severe multifocal [depth to tidemark] chondrocyte loss and/or collagen disruption).

Plasma IL-1Ra determination. Blood samples for determination of plasma levels of IL-1Ra were collected from the tail veins of isoflurane-anesthetized rats while they were still receiving infusions, just prior to being killed. Blood levels of IL-1Ra were measured in RA patients (n = 4) at various times after SC administration of a single dose (150 mg) of IL-1Ra. Samples were analyzed using an enzyme-linked immunosorbent assay method with an antibody to IL-1Ra, which was produced at R&D Systems (Minneapolis, MN). The sensitivity of the assay was 22 pg/ml.

Statistical analysis. Clinical data for ankle width in both models were analyzed by determining the area under the dosing curve, followed by analysis of variance. Paw weights (mean ± SEM) for each group were analyzed for differences using the Student’s t-test.
RESULTS

Effects of IL-1Ra on collagen-induced arthritis. Rats treated with 5, 1, 0.2, or 0.04 mg/kg/hour IL-1Ra by continuous SC infusion had mean (±SEM) serum levels of IL-1Ra ranging from 5.50 ± 0.53 µg/ml to 0.031 ± 0.008 µg/ml (Figure 1A). Inhibition of final paw weights was significant in rats given 5, 1, or 0.2 mg/kg/hour IL-1Ra, with inhibitions of 90%, 62%, and 35%, respectively (Figure 1B). Evaluation of the data as the area under the curve for ankle joint width over time also revealed dramatic suppression of arthritis (Figures 1C and D), with inhibitions of 90%, 53%, and 32% at the 5, 1, and 0.2 mg/kg/hour doses, respectively. Histologic evaluation of inflammation, pannus formation, cartilage damage, and bone lesions in the ankle joints of these rats confirmed the dose-related suppression of clinical arthritis (Figures 2A and B).

Effects of IL-1Ra on adjuvant arthritis. Rats treated with 10, 5, 2.5, or 1 mg/kg/hour IL-1Ra by continuous IV infusion had mean (±SEM) serum levels ranging from 14.95 ± 3.12 µg/ml to 1.19 ± 0.163 µg/ml (Figure 3A). The blood levels of IL-1Ra were similar to those seen in collagen-induced arthritis rats given similar infusion doses (Figure 1A). Inhibition of final paw weights was significant only in rats given 10, 5, or 2.5 mg/kg/hour IL-1Ra, with inhibitions of 18–23% (Figure 3B). Evaluation of the data as the area under the curve for ankle joint width over time also revealed only...
modest effects on inhibition of inflammation (Figures 3C and D).

In contrast, histologic evaluation of ankle joints indicated that IL-1Ra treatment at doses as low as 1 mg/kg/hour provided 49% inhibition of bone resorption (Figure 4A). Osteoclast numbers were significantly reduced in the adjuvant arthritis rats treated with 10, 5, or 2.5 mg/kg/hour, with inhibitions ranging from 83% to 99% (Figure 4B). Rats treated with the 1 mg/kg/hour dose had 43% (nonsignificant) inhibition of osteoclast activation. Significant differences in the intensity of histologic inflammation were not seen with any dose of IL-1Ra tested (Figure 4A).

**Plasma levels of IL-1Ra in RA patients.** The peak mean level of IL-1Ra in RA patients after a single SC injection of 150 mg (~2 mg/kg) was 1.6 μg/ml at 6 hours after dosing (Figure 5), and fell below 1.0 μg/ml at 18 hours after injection.

**DISCUSSION**

IL-1 appears to be a major mediator of type II collagen-induced arthritis in rats. Nearly complete (90%) suppression of established arthritis was achieved when rats were treated with continuous SC infusion doses of 5 mg/kg/hour (serum levels 5.5 μg/ml). The importance of maintaining blood levels was emphasized by the reduced efficacy of IL-1Ra in rats treated with doses that resulted in plasma levels of 1 μg/ml or less. The maximally effective dose of 5 mg/kg/hour dramatically suppressed all aspects of the arthritis, ranging from clinical signs to histologic changes. Theoretically, collagen-induced arthritis is the more challenging model in which to demonstrate a therapeutic impact, since treatment is initiated when disease is established. However, prophylactic treatment of adjuvant arthritis rats with similar and even higher doses of IL-1Ra resulted in only modest inhibition of periarticular inflammation.

In other studies involving IL-1Ra (data not shown), we have occasionally seen inhibition as high as 50%, but in general, a dose of 5 mg/kg/hour, with plasma levels of ~5–6 μg/ml IL-1Ra, results in 5–25% inhibition of paw swelling. The absence of dramatic suppression of arthritis (according to swelling parameters) in rats...
treated with infusion doses as high as 10 mg/kg/hour (plasma levels 15 µg/ml) suggests that IL-1 is of minor importance in the pathogenesis of the inflammation in the adjuvant arthritis model. However, despite the absence of antiinflammatory activity, IL-1Ra treatment was able to markedly suppress bone resorption. These results suggest that IL-1 is a major mediator of the inflammation-induced bone loss in the adjuvant arthritis model.

Thus, both the developing adjuvant arthritis and established type II collagen–induced arthritis rat models show that treatment with IL-1Ra is beneficial in terms of achieving inhibition of bone resorption. IL-1Ra has also been shown to be effective in inhibiting ovariectomy-induced bone loss in rats when it is administered by continuous infusion via Alzet pumps (14).

IL-1 inhibition has resulted in variable efficacy in other rat models of arthritis. In the streptococcal cell wall–induced reactivated arthritis model, treatment of rats intraperitoneally with 2–3 mg/kg IL-1Ra prior to reactivation and then every 6 hours resulted in 55% inhibition of joint swelling over the 5-day study period (8). Higher doses of 8 mg/kg were effective when given every 12 hours. However, when the dosing interval was increased to 24 hours, IL-1Ra at doses up to 32 mg/kg was ineffective, thus emphasizing the need to maintain adequate blood levels on a continuous basis during the period of time in which IL-1 is important in the pathogenesis of the disease. That study also demonstrated that in the ideal dosing scenario of prophylactic treatment followed by regular injections to maintain blood levels, IL-1Ra treatment resulted in a maximal inhibition of soft tissue swelling of 60%. In the study, evaluation of bone resorption was not a major focus; however, the authors did report that bone and cartilage erosions were reduced by IL-1Ra treatment. Interestingly, when IL-1Ra treatment was given prior to reactivation and then 2 hours and 6 hours later with no further treatment, arthritis severity was enhanced. To account for this phenomenon, the authors speculated that IL-1 might be down-regulating some facets of the early inflammatory response.

Additional evidence of the role of IL-1 in the rat streptococcal cell wall–induced arthritis model comes from gene transfer studies. Retroviral-transfected synoviocytes carrying IL-1Ra complementary DNA engrafted into the ankle joints of rats prior to reactivation of streptococcal cell wall–induced arthritis significantly suppressed the severity of recurrent arthritis, as assessed by measuring joint swelling, and attenuated, but did not abolish, cartilage and bone damage (15).

The effects of IL-1 inhibition have been examined in several mouse models of arthritis. Treatment of antigen-induced arthritis mice with IL-1Ra administered by osmotic minipumps (~1.5 mg/kg/hour) provided 100% protection against arthritis-associated suppression of cartilage proteoglycan synthesis (2), as did treatment with an antibody to IL-1 (IL-1α and IL-1β). Repetitive intraperitoneal bolus doses up to 10 mg/kg were relatively ineffective, again emphasizing the need for maintenance of continuous, adequate blood levels for IL-1 receptor saturation. Interestingly, this continuous infusion exposure level would result in blood levels of ~3–4 µg/ml in the mice (Bendele A: unpublished data), roughly equivalent to the blood levels needed for maximal suppression of rat collagen-induced arthritis as shown in our study. In that model, IL-1 inhibition using IL-1Ra did not suppress the acute inflammation; however, the chronic inflammation was modestly suppressed. IL-1 inhibition by treatment with antibodies did provide some protection against the acute inflammation of antigen-induced arthritis (16).

Mice with immune complex arthritis had complete inhibition of inflammation-induced suppression of cartilage proteoglycan synthesis when IL-1Ra was given by continuous infusion (~1.7 mg/kg/hour) (17). Antibody treatment provided similar protection. In that model, IL-1Ra or antibody treatment also inhibited swelling (80–90%) and inflammatory cell infiltration into the joints.

The mouse model in which the most dramatic effects of IL-1 inhibition have been observed is that of type II collagen–induced arthritis. Treatment with either IL-1Ra (continuous infusion) or antibodies to IL-1 markedly suppresses the development of arthritis when treatments are prophylactic (18). Results similar to ours in established rat collagen–induced arthritis have also been observed in mice with established disease treated with IL-1Ra by continuous infusion (19). Interestingly, maintenance of IL-1Ra blood levels of ~3 µg/ml was necessary for maximal inhibition in both the rat model (our study) and the mouse model of collagen–induced arthritis. In that model, IL-1 inhibition was effective on all aspects of the type II collagen disease, i.e., clinical signs, cartilage metabolic integrity, and histology.

The prevailing question for pharmacologists who evaluate potential antiarthritic agents in animal models has always been, which model is most predictive of activity in humans? The adjuvant arthritis model has predicted the activity of a number of compounds that are currently used in the treatment of RA or are being tested in clinical trials. Interestingly, in the case of
nonsteroidal antiinflammatory drugs (NSAIDs) and cyclosporin A, the minimal effective dose in the adjuvant arthritis model is the clinical dose that has been used in humans. For example, daily doses of 0.3 mg/kg piroxicam or 5 mg/kg cyclosporin A will give ~40% inhibition of adjuvant arthritic soft tissue swelling and modest, if any, inhibition of bone resorption (Bendele A: unpublished data). Therefore, the adjuvant arthritis model would predict that these agents, given at these doses, will provide symptomatic antiinflammatory relief and very little disease modification. Higher doses of these agents will provide profound effects on all arthritis parameters, but with prolonged dosing at these higher levels, animals experience toxic reactions. Similarly, humans cannot tolerate the level of dosing that is necessary to induce disease modification in animals. If the adjuvant arthritis model is predictive of the effects of IL-1Ra, then the human clinical data should reveal moderate-to-marked suppression of bone resorption (assuming maintenance of blood levels of ~1 µg/ml), with only modest antiinflammatory effects.

With regard to the rat and mouse type II collagen–induced arthritis models, there have been very few historic data published on the comparative effects of currently used drugs. The NSAIDs have typically been active in rat collagen-induced arthritis at doses similar to those used in adjuvant arthritis (Bendele A: unpublished data). However, mice are relatively insensitive to their effects. Mouse collagen-induced arthritis has been a very popular test system for biologic agents, and its relevance will become more apparent as more clinical studies reach completion of the third phase. Both the rat and mouse type II collagen–induced arthritis models are very sensitive to IL-1 inhibition. If this model is predictive of the response in RA patients, then IL-1Ra should have dramatic effects on both soft tissue swelling and disease progression. However, maintenance of adequate blood levels on a continuous basis is important in determining the magnitude of effect, as evidenced by our data as well as by the data from others (19).

Results of a 24-week clinical study (7) revealed a profile of IL-1Ra activity that more closely resembles that seen in our adjuvant arthritis rats. Joint swelling and other indices of inflammation were modestly improved by treatment with a total daily dose of 150 mg. In that study, 43% of patients met the American College of Rheumatology criteria for response (the primary efficacy measure) at 24 weeks, and 44% met the Paulus criteria. In addition, the rate of radiologic progression in patients treated with IL-1Ra was less than that in the placebo group, as measured by the Larsen score. These effects were achieved with daily SC dosing, a regimen which would result in peak plasma levels of ~1.6 µg/ml at 6 hours after dosing, with levels falling to <1 µg/ml at 18 hours after treatment. These blood levels are in the range of values that would be predicted, based on the data from adjuvant arthritis rats, to give moderate anti–bone resorption effects with mild antiinflammatory effects. However, our data suggest that this kind of blood-level profile would result in modest inhibition of all parameters of type II collagen–induced arthritis. Therefore, the activity of IL-1Ra in humans could be similar to that of IL-1Ra in type II collagen–induced arthritis in rats under suboptimal dosing conditions.

The question then becomes, would blood levels ≥1 µg/ml maintained continuously in humans result in activity similar to the outstanding activity seen in collagen-induced arthritis rats when blood levels were maintained at 5 µg/ml? Or would the antiinflammatory activity remain modest (as is the case in adjuvant arthritis), despite optimal delivery? A clinical trial in which IL-1Ra is delivered to RA patients by continuous infusion or by a slow-release delivery system would address these questions.

REFERENCES


SUSTAINED BLOOD LEVELS OF IL-1Ra IN ARTHRITIS 505