Rheumatology 2002;41:972–980

Review

Blocking the effects of IL-1 in rheumatoid arthritis protects bone and cartilage

S. B. Abramson and A. Amin

Department of Rheumatology, Hospital for Joint Diseases, New York University of Medicine, 301 East 17th Street, New York, NY 10003, USA

Abstract

Destruction of articular joints occurs progressively in patients with rheumatoid arthritis (RA). Although the exact aetiology of RA has not been fully elucidated, a large body of evidence supports a role for interleukin-1 (IL-1) in cartilage and bone erosion. *In vitro* studies suggest that IL-1 can cause cartilage destruction by stimulating the release of matrix metalloproteinases and other degradative products, and it can increase bone resorption by stimulating osteoclast differentiation and activation. In animal models of RA, blocking the effects of IL-1 with either IL-1 receptor antagonist (IL-1Ra; endogenous), anti-IL-1 monoclonal antibodies, or soluble IL-1 type II receptors significantly reduced cartilage destruction and bone erosion. Gene therapy with IL-1Ra was also effective in reducing joint destruction in experimental RA and osteoarthritis (OA) models. In clinical studies, anakinra, a human recombinant IL-1 receptor antagonist (IL-1ra; exogenous), significantly slowed radiographic progression of RA relative to placebo and significantly reduced clinical symptoms when used as monotherapy or in addition to existing methotrexate therapy. These results demonstrate that blocking IL-1 protects bone and cartilage from progressive destruction in RA.

Destruction of bone and cartilage in articular joints occurs progressively in RA and ultimately leads to significant disability [1, 2]. Many patients with RA have radiographic evidence of substantial joint damage within the first 2 yr of disease [3], and even in the first few months evidence of bone erosion may be seen with magnetic resonance imaging [4, 5]. Damage to articular cartilage in RA begins at the cartilage–pannus interface, with progressive erosions occurring into subchondral bone. The pattern of bone damage in the joint includes focal erosions and juxta-articular osteopenia. The impact of RA on bone, however, is also observed systemically in the axial and appendicular skeleton, with reductions in bone mineral density causing osteoporosis and, as a consequence, increased risk of fracture [6, 7].

The exact aetiology of RA remains unknown, but the first signs of joint disease appear in the synovial lining layer, with proliferation of synovial fibroblasts and their attachment to the articular surface at the joint margin [8]. Subsequently, macrophages, T cells and other inflammatory cells are recruited into the joint, where they produce a number of mediators, including the cytokines interleukin-1 (IL-1), which contributes to the chronic sequelae leading to bone and cartilage destruction, and tumour necrosis factor (TNF-α), which plays a role in inflammation [9–11]. The concentration of IL-1 in plasma is significantly higher in patients with RA than in healthy individuals and, notably, plasma IL-1 levels correlate with RA disease activity [12]. Moreover, synovial fluid levels of IL-1 are correlated with various radiographic and histologic features of RA [13, 14].

In normal joints, the effects of these and other proinflammatory cytokines are balanced by a variety of anti-inflammatory cytokines and regulatory factors [15]. The significance of this cytokine balance is illustrated in juvenile RA patients, who have cyclical increases in fever throughout the day [16]. After each peak in fever, a factor that blocks the effects of IL-1 is found in serum and urine. This factor has been isolated, cloned and identified as IL-1 receptor antagonist (IL-1Ra), a member of the IL-1 gene family [17]. IL-1Ra, as its name indicates, is a natural receptor antagonist that competes with IL-1 for binding to type I IL-1 receptors and, as a result, blocks the effects of IL-1 [18]. A 10- to 100-fold excess of IL-1Ra may be needed to block IL-1 effectively; however, synovial cells isolated from patients with RA do not appear to produce enough IL-1Ra to counteract the effects of IL-1 [19, 20]. This review will discuss the role of IL-1 and the impact of blocking this cytokine on the joint destruction seen in RA.

Submitted 2 August 2001; revised version accepted 15 March 2002.

Correspondence to: S. B. Abramson.

In vitro studies in cartilage and bone

Cartilage

Articular cartilage consists of a highly structured extracellular matrix composed primarily of type II collagen and proteoglycans that account for the tensile strength and load-bearing capacity of the joint. Chondrocytes are embedded within this matrix; these cells participate in the degradation of the extracellular matrix as well as in the synthesis of new matrix proteins. Under normal conditions, these processes are maintained in balance by various cytokines and growth factors. In RA and OA, however, this balance is tipped in favour of net matrix destruction. Although the clinical features of these arthritic diseases differ, IL-1 is believed to play a central role in the cartilage destruction inherent to both disorders.

In RA, IL-1 stimulates the release of degradative enzymes by synovial fibroblasts at the cartilage–pannus interface. IL-1 also activates chondrocytes to release these enzymes, which probably contributes to the cartilage destruction seen in both OA and RA at sites distant to the pannus. The most important enzymes involved in cartilage destruction are a family of zinc-dependent matrix metalloproteinases (MMPs) [21, 22]. The various members of the MMP family target different components of extracellular matrix. Collagenase degrades collagen; collagenase-3, also known as MMP-13, may be particularly important because of its ability to degrade type II collagen [23]. Stromelysins degrade proteoglycans and activate latent collagenases, whereas gelatinases further degrade collagen that has already been clipped by collagenase. In addition to MMPs, IL-1 stimulates the production of nitric oxide and prostaglandin E_2 (PGE_2) from articular chondrocytes; these mediators probably contribute to the cartilage destruction seen in arthritis [24, 25]. Moreover, in addition to stimulating matrix degradation, IL-1 simultaneously inhibits the synthesis of matrix proteins, including type II collagen, other collagen proteins and the large proteoglycan, aggrecan.

Cartilage damage in arthritis occurs initially in the superficial layers. Interestingly, chondrocytes isolated from these superficial layers appear more susceptible to IL-1 than those found in deeper layers [26]. When chondrocytes from the superficial and deeper layers were cultured and stimulated with IL-1, greater release of MMPs and greater inhibition of proteoglycan synthesis were observed in superficial chondrocytes. These cells also had higher levels of high-affinity IL-1 receptors than those isolated from deeper layers. Notably, IL-1Ra was more effective in blocking the deleterious effects of IL-1 in the deeper layers, presumably due to their lower number of IL-1 receptors.

Cartilage degradation *in vitro* is inhibited by agents that block the effects of IL-1. For example, the process of cartilage invasion by synovial fibroblasts in RA was modelled in a culture of human chondrocytes, which were implanted in sponges pretreated with embryonic extracellular matrix [27]. In this culture system, a cartilaginous matrix developed with incorporation of proteoglycans. Addition of RA synovial fibroblasts destroyed the matrix as reflected by proteoglycan release, and this process was augmented by addition of IL-1β. In contrast, addition of IL-1Ra or an anti-IL-1β monoclonal antibody reduced the synovial fibroblast-mediated destruction by up to 45%. In another study, IL-1-induced proteoglycan degradation was measured in an organ culture system, in which OA chondrocytes were seeded onto the surface of OA cartilage [28]. When chondrocytes carrying an IL-1Ra transgene were seeded onto the cartilage, IL-1-induced proteoglycan release was almost completely inhibited.

Cartilage from patients with arthritis shows upregulation of IL-1β mRNA as compared with normal cartilage [29]. In culture, OA cartilage spontaneously releases detectable levels of IL-1, nitric oxide and PGE_2 [25, 30, 31]. Sufficient IL-1 is produced spontaneously to modulate the production of nitric oxide and PGE_2. The nitric oxide synthase inhibitor N^G-monomethyl-L-arginine produced a marked increase in IL-1Ra synthesis, suggesting that spontaneous release of NO from arthritic cartilage may reduce IL-1Ra production by chrondrocytes [24].

Bone

Bone remodelling is a normal process that allows the skeleton to adapt to local biomechanical changes and to repair microdamaged regions [32]. This process requires coordination between osteoclasts, which resorb bone, and osteoblasts, which deposit mineral and matrix in previously resorbed areas. When new bone formation matches bone resorption, bone mass is maintained. However, when bone remodelling is not regulated appropriately, evidence of bone loss is observed. On the basis of histopathologic analyses and markers of bone metabolism, the bone erosions occurring in the early stages of RA appear as a result of an increase in osteoclast-mediated resorption that is not matched by new bone formation [33]. In patients with RA, osteoclast-mediated bone resorption is evident at the pannus–bone interface as well as in subchondral bone [34–36].

The recruitment of osteoclasts to the bone surface is an integral step in bone remodelling [32]. Osteoclasts, which are the only cells known to resorb bone, are derived from haematopoietic stem cells that also give rise to the monocyte-macrophage lineage. These stem cells differentiate into osteoclast precursor cells and subsequently into fully functional osteoclasts. This process is regulated by receptor activator of NF-κB ligand (RANKL)/osteoclast differentiation factor (ODF) and osteoprotegerin (OPG) [37, 38]. IL-1, as well as a number of other factors including 1,25-dihydroxyvitamin D_3, parathyroid hormone, TNF-α and PGE_2 increase RANKL/ODF in osteoblasts and bone lining cells. RANKL/ODF binds to receptor activator of NF-κB (RANK) on osteoclast precursor cells to stimulate

osteoclast differentiation, and on osteoclasts to increase their resorptive activity [38]. IL-1 also regulates production of OPG, which is a natural inhibitor of RANKL/ODF. OPG binds to RANKL/ODF and consequently inhibits its ability to bind to RANK on osteoclast precursor cells or osteoclasts. Interestingly, administration of OPG to animals with inflammatory arthritis leads to inhibition of focal bone erosions, suggesting that RANKL/ODF plays an important role in osteoclast-mediated bone resorption in RA [40].

In organ cultures of murine calvaria and rat long bones, IL-1Ra has been shown to reduce IL-1-induced bone resorption but not that caused by parathyroid hormone or TNF-α [41], and IL-1Ra has also been shown to block formation of osteoclast-like cells in murine marrow cultures in response to IL-1 or ovariectomy [42, 43]. These *in vitro* studies demonstrate that blocking the effect of IL-1 leads to a reduction in bone resorption. Clinical trials with anakinra demonstrate that blocking the effects of IL-1 protects bone and cartilage in RA. Clinical trials and studies of the effects of blocking IL-1 on bone resorption in animal models will be described in the following sections.

Animal models of RA

IL-1 overexpression and deficiency

Intra-articular expression of IL-1 causes arthritis in animals [44]. When the human IL-1β gene was transfected into synoviocytes and then transferred into a rabbit knee joint, high-level expression of human IL-1β was detectable within 1–2 weeks, but had declined significantly by 4 weeks. The production of human IL-1β was accompanied by production of endogenous rabbit IL-1 and TNF-α. During this period of human IL-1β expression, the following arthritic features were evident: presence of synovial hypertrophy and hyperplasia, profound increase in leucocyte infiltration into the joint space, presence of high levels of cartilage breakdown products in joint fluid, and reduced synthesis of extracellular matrix components. In addition, systemic manifestations were present, including fever, increased erythrocyte sedimentation rate (ESR) and weight loss. In the first week after introduction of the IL-1β transgene, the synovium had attached to cartilage and subchondral bone, and initial evidence of erosions into cortical bone was observed. In the next week, pannus had invaded into cartilage and subchondral bone, producing severe erosions of cortical bone. By 2–3 weeks, pannus invasiveness had reached into the bone marrow. Thus, overexpression of human IL-1β in the rabbit knee joint produced clinical and histopathologic features characteristic of RA.

A role of IL-1 in joint destruction is also evident in IL-1-deficient mice. When streptococcal cell-wall (SCW) arthritis was induced in IL-1-deficient mice, cartilage damage and sustained cellular infiltration in the synovium were greatly reduced relative to arthritis in wild-type controls [45]. Joint swelling, however, was not reduced in these IL-1-deficient mice. Repeated administration of small amounts of streptococcal cell walls at sites of ongoing arthritis produces arthritis episodes. When this chronic relapsing model of arthritis was evaluated in IL-1-deficient mice, cartilage erosion was essentially abolished and the synovial infiltrate was significantly reduced. These results suggest that IL-1 may produce joint damage in the SCW arthritis model, whereas inflammation is caused by additional mechanisms.

Another study in SCW arthritis was conducted to determine whether blocking the actions of cytokines IL-1 and TNF-α would result in decreased inflammation. Results showed that blocking TNF with antibodies effectively reduced swelling with little effect on cartilage and bone degradation, while treatment with IL-1 antibodies resulted in little or no suppression of inflammation, but did result in normalization of chondrocyte activity [11]. These data suggest that TNF, at least in this murine model, plays a more active role in inflammation while IL-1 functions in cartilage and bone degradation.

IL-1Ra deficiency

Deletion of the IL-1Ra gene leads to the spontaneous development of a chronic polyarthropathy in BALB/cA mice [46]. The incidence of arthritis was 80% at 8 weeks of age and 100% at 16 weeks of age, with signs of inflammation being more pronounced in hind limbs than in the front paws. Pathologically, the polyarthritis was characterized by synovial hyperplasia, leucocytic infiltration and erosive pannus formation. IL-1β levels were 10-fold higher in the IL-1Ra-deficient animals than in controls, whereas TNFα levels were only slightly increased. However, in C57BL/6J mice, the impact of IL-1Ra gene deletion was less pronounced as only 15% of animals developed arthritis by 32 weeks. These results support a role for IL-1Ra in maintaining a balance with IL-1 in the joint, at least in animals with certain genetic backgrounds.

IL-1 blockade and therapeutic effect

Blocking IL-1 has been shown to reduce joint destruction in animal models of RA. In one study, mice with collagen-induced arthritis were treated on day 28 with a single injection of rabbit anti-IL-1α/β [47]. Treatment with anti-IL-1 was associated with significant reductions in clinical score and in circulating levels of the cartilage turnover marker, cartilage oligomeric matrix protein. Notably, radiographic assessment showed that anti-IL-1 treatment abolished bone erosions of knee and ankle joints. Moreover, histopathologic assessment showed that anti-IL-1 almost completely prevented cellular infiltration, cartilage damage, matrix proteoglycan depletion, and bone erosions (Fig. 1). Finally, a marker of MMP-mediated aggrecan cleavage was almost absent in the cartilage of animals treated with anti-IL-1. In this study, a group of animals were treated

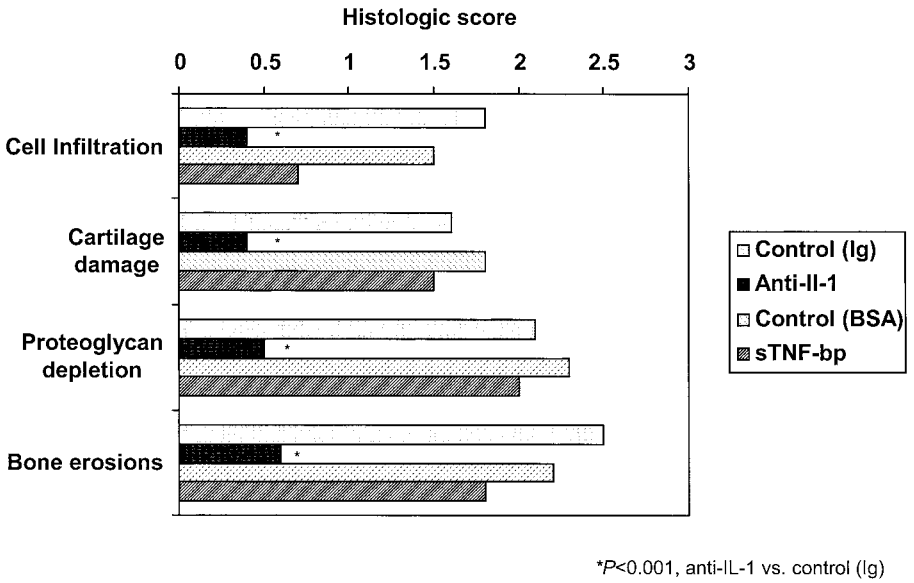

FIG. 1. Effect of anti-IL-1 on histologic analysis of knee joints of mice with collagen-induced arthritis. Mice were treated with a single dose of 1 mg rabbit anti-IL-1 or with 3 mg/kg soluble TNF binding protein (sTNF-bp) every other day, starting after disease onset on day 28. For the histologic analysis on day 36, joints were decalcified, dehydrated and embedded in paraffin, and then standard 7-μm sections were stained with either haematoxylin–eosin or with safranin O. Sections were then scored by two observers on a scale of 0–3 for cellular infiltration, cartilage damage, proteoglycan depletion and bone erosions. *$P<0.001$ compared with control by the Mann–Whitney U-test. Adapted from Joosten *et al.* [47].

every other day with a soluble TNF-α binding protein. In these animals, joint inflammation was reduced, but cartilage and bone destruction were not prevented.

In another study, histopathologic assessment of ankle joints from control rats with adjuvant arthritis showed obvious resorption of medullary trabecula and cortical bone, loss of some medullary trabeculae, and presence of numerous osteoclasts [48]. However, when IL-1ra was administered at doses of 2.5 to 10 mg/kg/h via a continuous intravenous infusion, bone resorption was significantly reduced by 79 to 85% relative to control animals. The antiresorptive effect of IL-1ra was accompanied by a significant reduction in the number of osteoclasts. In this study, IL-1ra was given for 1 week, starting on day 8 after administration of adjuvant, which is 1–2 days before any clinical manifestations of arthritis are generally observed. Interestingly, IL-1ra inhibited bone resorption in these arthritic rats without significantly affecting the histopathologic assessment of inflammation in the ankle joints. Continuous intravenous administration of IL-1ra at doses of 1–5 mg/kg/h to rats with collagen-induced arthritis, starting as soon as signs of arthritis developed, significantly reduced histopathologic evidence of bone resorption, pannus formation, cartilage damage and inflammation [48]. The overall histopathologic score was reduced by 89% at the highest IL-1ra dose tested.

Another approach to blocking the effects of IL-1 is to use soluble type II IL-1 receptors (sIL-1RII). In an antigen-induced arthritis model in rabbits, sIL-1RII was administered via an intravenous bolus followed by subcutaneous dosing via mini-pump for 14 days starting at the time that arthritis was induced [49]. Synovial fluid levels of IL-1α and IL-β were reduced dose-dependently by sIL-1RII. At the highest dose tested, sIL-1RII also significantly reduced histologic evidence of soft tissue swelling and joint damage. Thus, three different agents that block IL-1—anti-IL-1, IL-1Ra and sIL-1RII—have demonstrated the ability to reduce joint destruction in animal models of RA. sIL-1RII has recently been shown to effectively inhibit the spontaneous production of NO by human OA explant cultures [50].

Gene transfer of IL-1Ra

Gene transfer of IL-1Ra has been evaluated in several models of RA and OA. In rats with chronic relapsing SCW arthritis, joint diameter was reduced significantly in ankle joints expressing the IL-1Ra transgene, but not in contralateral joints in response to rechallenge with streptococcal cell walls [51]. Notably, erosion of cartilage and subchondral bone was reduced significantly but not abolished in joints expressing the transgene. The IL-1Ra gene was also transduced into RA synovial fibroblasts and then co-implanted with normal human cartilage in severe combined immunodeficiency (SCID) mice [52]. The transgene continued to secrete IL-1Ra over a 60-day period. Progressive, chondrocyte-mediated cartilage degradation was evident in control mice transplanted with synovial fibroblasts containing a marker transgene. However, cartilage degradation was not observed in mice receiving synoviocytes carrying the IL-1Ra transgene. Finally, in antigen-induced arthritis in rabbits, IL-1Ra gene

therapy nearly normalized cartilage matrix destruction and new matrix synthesis [53]. Of the indices of inflammation that were evaluated, only leucocyte infiltration into the joint space was reduced by the IL-1Ra transgene.

The effect of IL-1Ra gene transfer has also been assessed in an experimental OA model in dogs [54]. The anterior cruciate ligament of the right knee was sectioned and, 2 days later, synovial fibroblasts carrying the human IL-1Ra gene or a control β-galactosidase gene were injected intra-articularly. High levels of IL-1Ra were detected in synovial fluid at 2 weeks in animals receiving the IL-1Ra transgene. At 4 weeks the dogs were sacrificed, and the knees were dissected and evaluated macroscopically and histologically. Dogs receiving the IL-1Ra transgene showed a marked reduction in macroscopic and histologic lesion severity on the tibial plateaus and femoral condyles compared with animals receiving the control transgene and control animals receiving a sham injection of phosphate-buffered saline. Similar evidence of cartilage protection with IL-1Ra gene therapy has been observed in a meniscectomy model of OA in rabbits [55].

Therapeutic effects of IL-1 blockade in clinical trials

The relative deficiency of IL-1Ra in the rheumatoid joint and the efficacy of anakinra (IL-1ra) in animal models of RA prompted the clinical evaluation of anakinra, a recombinant human IL-1ra [56]. Anakinra is identical to the naturally occurring non-glycosylated form of IL-1Ra, with the exception of one N-terminal methionine. Monotherapy with anakinra was evaluated in a randomized, controlled, European multicentre study [56]. A total of 472 patients meeting American College of Rheumatology (ACR) criteria for RA, with symptoms for 0.5–8 yr and typical features of active disease (i.e. the presence of 10 or more swollen joints and two of the following criteria: 10 or more tender or painful joints, severe or very severe disease activity on physician assessment, or C-protein level >1.5 mg/dl), were randomly assigned to receive anakinra 30, 75 or 150 mg or placebo once daily by s.c. injection for 24 weeks. Previous disease-modifying anti-rheumatic drug (DMARD) therapy was withdrawn at least 6 weeks before the first dose of anakinra. Patients completing the 24-week treatment period were eligible to continue anakinra therapy for a second 24-week period.

The four treatment arms of this study were well balanced at baseline: patients averaged 52–54 yr of age, with the majority being female (70–79%) and seropositive for rheumatoid factor (69–71%) [56]. The mean duration of RA in the four groups ranged from 3.7 to 4.3 yr, with most patients (69–77%) having evidence of bone erosions at baseline. Usage of NSAIDs (82–89%) and corticosteroids (41–49%) was comparable among the treatment arms. Previous DMARD usage was 66–81%, with the lowest percentage seen in the anakinra 150 mg group; however, previous DMARD use was not predictive of response to treatment. Disease severity was also comparable among the four groups in terms of mean swollen joint counts (26–27), tender joint counts (33–36), ESR values (47–53 mm/h) and C-reactive protein values (4.0–4.2 mg/dl).

After 24 weeks of treatment, anakinra provided significantly greater clinical improvement than placebo. The ACR 20% composite index [57] was the primary efficacy measure: a significantly higher percentage of patients in the anakinra 150 mg group than in the placebo group responded to treatment according to these criteria

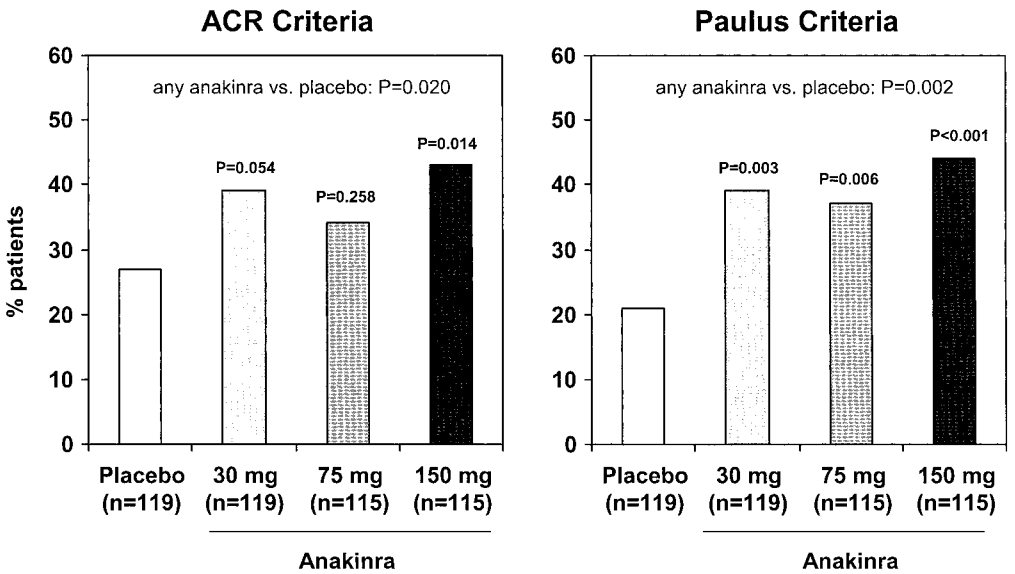

FIG. 2. Clinical response to anakinra according to ACR 20% criteria and Paulus criteria for improvement in RA. Patients with active RA were treated with anakinra 30, 75 or 150 mg, or placebo once daily via subcutaneous injection for 24 weeks. Adapted from Bresnihan *et al.* [56].

(43% versus 27%; $P=0.014$) (Fig. 2). Moreover, the three anakinra doses combined were also significantly more effective than placebo ($P=0.020$). Notably, anakinra 150 mg and the anakinra doses combined were significantly better than placebo for all ACR clinical parameters. When the Paulus criteria for RA improvement [58] were used, each anakinra dose was significantly superior to placebo ($P \leqslant 0.003$). In addition, statistically significant improvements relative to placebo were observed in each anakinra group for Health Assessment Questionnaire score ($P \leqslant 0.05$) [59], C-reactive protein ($P \leqslant 0.004$) and ESR ($P \leqslant 0.0005$).

The impact of anakinra therapy on bone erosions and joint space narrowing was also evaluated in this study [60]. Hand radiographs taken at baseline and after 24 weeks of treatment were scored according to the Genant method [61]. Erosions in 28 joints were scored on a scale of 0–3.5, and joint space narrowing in 26 joints was scored on a scale of 0–4, for a maximum total score of 202. Radiographic progression of disease during the 24-week treatment period was evident in the placebo group: the mean change from baseline in total Genant score was 3.52. In comparison, radiographic progression was slowed significantly in each anakinra group: the changes from baseline ranged from 1.87 with anakinra 30 mg to 1.81 with anakinra 150 mg ($P \leqslant 0.004$) (Fig. 3). Moreover, anakinra 30 mg and 150 mg significantly lowered the progression in bone erosion score relative to placebo ($P \leqslant 0.03$), and all three doses significantly reduced the progression in joint space narrowing score relative to placebo ($P \leqslant 0.008$). The hand radiographs were also evaluated according to the Larsen method [62], in which 30 joints were scored globally on a scale of 0–5, and erosive joint counts were determined by the number of joints with definite bone erosion (defined by a score $\geqslant 2$). The change from baseline of the Larsen score was 6.22 with placebo and 3.76 with any anakinra treatment ($P=0.03$). Notably, the progression in Larsen erosive joint count was significantly reduced by any anakinra therapy compared with placebo (1.44 versus 2.62; $P=0.0005$).

In the 24-week extension period, radiographic progression appeared to slow further, particularly in the anakinra 75 mg and 150 mg groups. Whereas the benefit of anakinra was more evident on joint space narrowing during the first 24 weeks, a greater effect on erosions was seen during the period between 24 and 48 weeks. In the anakinra groups combined, the mean change in joint space narrowing score was 0.6 during each 24-week period, whereas the mean change in erosions was 1.2 during the first 24 weeks and 0.6 during the 24-week extension period ($P=0.0001$).

Anakinra has also been evaluated in combination with methotrexate in a 24-week, double-blind, placebo-controlled study [63]. A total of 419 patients who had active RA despite methotrexate therapy for at least 6 months and who had received a stable dose of methotrexate 12.5–25 mg weekly for at least 3 months participated in the study. Patients were randomly assigned to receive anakinra 0.04, 0.1, 0.4, 1.0 or 2.0 mg/kg or placebo administered once daily via subcutaneous injection. All patients continued to receive their existing methotrexate therapy. Despite the mean methotrexate dose of 17 mg weekly, patients had a mean of 25 tender joints and 18 swollen joints at baseline. After 24 weeks of treatment, 42% of patients in the anakinra 1.0-mg/kg group and 35% of those in the anakinra 2.0-mg/kg group achieved ACR 20% criteria, as compared with 23% of those in the placebo group ($P=0.021$ for anakinra 1.0 mg/kg versus placebo).

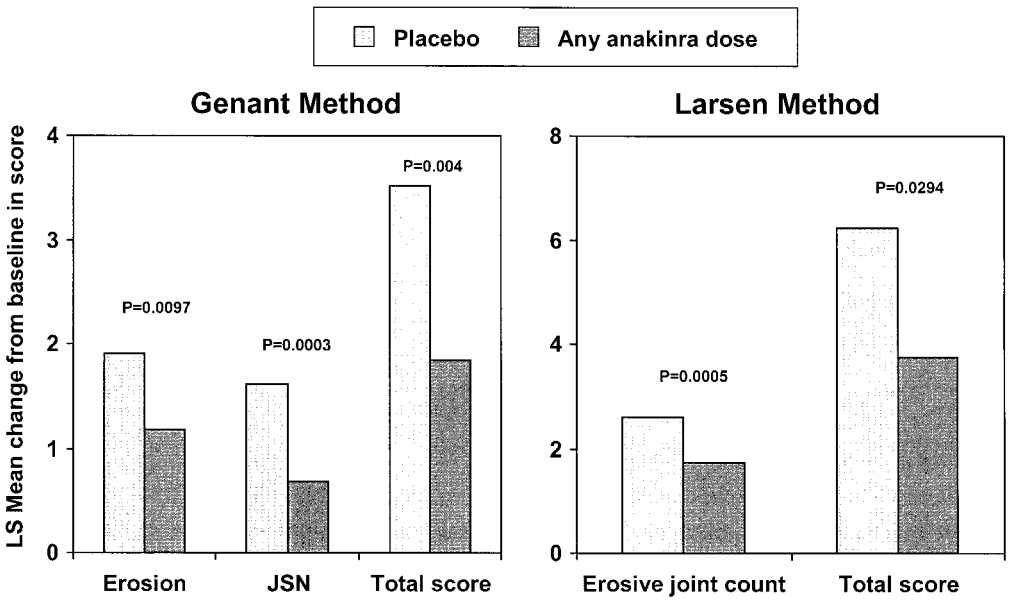

FIG. 3. Change from baseline in radiographic score after treatment with anakinra or placebo. Hand radiographs were assessed at baseline and after 24 weeks of treatment by the Genant and Larsen methods. The anakinra data represent patients treated with one of three doses: 30, 75 or 150 mg. Adapted from Jiang *et al.* [60].

Notably, 24 and 10% of patients treated with anakinra 1.0 mg/kg achieved ACR 50 and 70% responses, respectively. In addition, anakinra 1.0 and 2.0 mg/kg significantly improved the HAQ index, suggesting that the addition of anakinra to methotrexate improved the quality of life of these RA patients.

Conclusions

Evidence in animal models of RA with IL-1ra, anti-IL-1 and sIL-1RII, and in clinical trials with anakinra demonstrate that blocking the effects of IL-1 protects bone and cartilage from the destructive processes inherent to RA. The ability of anakinra to significantly slow radiographic progression supports the concept that IL-1 causes bone and cartilage erosion in RA. More importantly, these findings suggest that anakinra may offer the potential to alter the natural history of this disease, in as much as radiographic progression is ultimately correlated with functional and work disability [2]. Anakinra also provided significant improvements in clinical signs and symptoms when given as monotherapy or when added to existing methotrexate therapy. Based on trials of various DMARDs, clinical improvement does not necessarily predict slowing of radiographic progression and, consequently, both clinical and radiographic parameters need to be evaluated when the benefits of arthritis treatment are considered.

The presence of substantial bone erosions in many patients with early-stage RA underscores the need for early aggressive treatment. By slowing radiographic progression, it may be possible to prevent or delay the onset of disability and various comorbid conditions, such as osteoporosis. The availability of new biological therapies that target specific cytokines involved in joint destruction will probably usher in a new era in the treatment of RA. Clearly, epidemiological studies will be needed to document the long-term benefits and risks associated with blocking IL-1.

Acknowledgement

This work was supported in part by a grant from Amgen, Inc. (Thousand Oaks, CA 91320, USA).

References

1. Pincus T. Long-term outcomes in rheumatoid arthritis. Br J Rheumatol 1995;34(Suppl. 2):59–73.
2. Scott DL, Pugner K, Kaarela K *et al.* The links between joint damage and disability in rheumatoid arthritis. Rheumatology 2000;39:122–32.
3. Fuchs HA, Kaye JJ, Callahan LF, Nance EP, Pincus T. Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. J Rheumatol 1989;16:585–91.
4. McGonagle D, Conaghan PG, O'Connor P *et al.* The relationship between synovitis and bone changes in early untreated rheumatoid arthritis: a controlled magnetic resonance imaging study. Arthritis Rheum 1999; 42:1706–11.
5. Klarlund M, Ostergaard M, Jensen KE, Madsen JL, Skjodt H, Lorenzen I. Magnetic resonance imaging, radiography, and scintigraphy of the finger joints: one year follow up of patients with early arthritis. Ann Rheum Dis 2000;59:521–8.
6. Hooyman JR, Melton LJ, Nelson AM, O'Fallon WM, Riggs BL. Fractures after rheumatoid arthritis. A population-based study. Arthritis Rheum 1984;27:1353–61.
7. Spector TD, Hall GM, McCloskey EV, Kanis JA. Risk of vertebral fracture in women with rheumatoid arthritis. BMJ 1993;306:558.
8. Lipsky PE. Rheumatoid arthritis. In: Fauci AS, Braunwald E, Isselbacker KJ *et al.*, eds. Harrison's principles of internal medicine. 14th edn. New York: McGraw-Hill, 1998, pp. 1880–8.
9. Dinarello CA. Interleukin-1, interleukin-1 receptors and interleukin-1 receptor antagonist. Int Rev Immunol 1998;16:457–99.
10. Arend WP, Dayer JM. Inhibition of the production and effects of interleukin-1 and tumor necrosis factor alpha in rheumatoid arthritis. Arthritis Rheum 1995;38:151–60.
11. van den Berg WB. Uncoupling of inflammatory and destructive mechanisms in arthritis. Semin Arthritis Rheum 2001;30(5 Suppl. 2):7–16.
12. Eastgate JA, Symons JA, Wood NC, Grinlinton FM, di Giovine FS, Duff GW. Correlation of plasma interleukin 1 levels with disease activity in rheumatoid arthritis. Lancet 1988;2:706–9.
13. Kahle P, Saal JG, Schaudt K, Zacher J, Fritz P, Pawelec G. Determination of cytokines in synovial fluids: correlation with diagnosis and histomorphological characteristics of synovial tissue. Ann Rheum Dis 1992;51:731–4.
14. Rooney M, Symons JA, Duff GW. Interleukin 1 beta in synovial fluid is related to local disease activity in rheumatoid arthritis. Rheumatol Int 1990;10:217–9.
15. Burger D, Dayer JM. Inhibitory cytokines and cytokine inhibitors. Neurology 1995;45(6 Suppl. 6):S39–43.
16. Prieur AM, Kaufmann MT, Griscelli C, Dayer JM. Specific interleukin-1 inhibitor in serum and urine of children with systemic juvenile chronic arthritis. Lancet 1987;2:1240–2.
17. Hannum CH, Wilcox CJ, Arend WP *et al.* Interleukin-1 receptor antagonist activity of a human interleukin-1 inhibitor. Nature 1990;343:336–40.
18. Arend WP, Malyak M, Guthridge CJ, Gabay C. Interleukin-1 receptor antagonist: role in biology. Annu Rev Immunol 1998;16:27–55.
19. Firestein GS, Boyle DL, Yu C *et al.* Synovial interleukin-1 receptor antagonist and interleukin-1 balance in rheumatoid arthritis. Arthritis Rheum 1994;37:644–52.
20. Fujikawa Y, Shingu M, Torisu T, Masumi S. Interleukin-1 receptor antagonist production in cultured synovial cells from patients with rheumatoid arthritis and osteoarthritis. Ann Rheum Dis 1995;54:318–20.
21. Johnson LL, Dyer R, Hupe DJ. Matrix metalloproteinases. Curr Opin Chem Biol 1998;2:466–71.
22. Konttinen YT, Ainola M, Valleala H *et al.* Analysis of 16 different matrix metalloproteinases (MMP-1 to MMP-20) in the synovial membrane: different profiles in trauma and rheumatoid arthritis. Ann Rheum Dis 1999;58:691–7.
23. Reboul P, Pelletier JP, Tardif G, Cloutier JM, Martel-Pelletier J. The new collagenase, collagenase-3, is expressed and synthesized by human chondrocytes but

not synoviocytes. A role in osteoarthritis. J Clin Invest 1996;97:2011–9.
24. Pelletier JP, Mineau F, Ranger P, Tardif G, Martel-Pelletier J. The increased synthesis of inducible nitric oxide inhibits IL-1ra synthesis by human articular chondrocytes: possible role in osteoarthritic cartilage degradation. Osteoarthritis Cartilage 1996;4:77–84.
25. Amin AR, Attur M, Abramson SB. Cox-2, NO and cartilage damage and repair. Curr Opin Rheumatol 2002; 2:447–53.
26. Hauselmann HJ, Flechtenmacher J, Michal L *et al.* The superficial layer of human articular cartilage is more susceptible to interleukin-1-induced damage than the deeper layers. Arthritis Rheum 1996;39:478–88.
27. Neidhart M, Gay RE, Gay S. Anti-interleukin-1 and anti-CD44 interventions producing significant inhibition of cartilage destruction in an *in vitro* model of cartilage invasion by rheumatoid arthritis synovial fibroblasts. Arthritis Rheum 2000;43:1719–28.
28. Baragi VM, Renkiewicz RR, Jordan H, Bonadio J, Hartman JW, Roessler BJ. Transplantation of transduced chondrocytes protects articular cartilage from interleukin 1-induced extracellular matrix degradation. J Clin Invest 1995;96:2454–60.
29. Attur MG, Patel IR, Patel RN, Abramson SB, Amin AR. Autocrine production of IL-1 beta by human osteoarthritis-affected cartilage and differential regulation of endogenous nitric oxide, IL-6, prostaglandin E_2, and IL-8. Proc Assoc Am Physicians 1998;110:65–72.
30. Amin AR, Attur M, Patel RN *et al.* Superinduction of cyclooxygenase-2 activity in human osteoarthritis-affected cartilage. Influence of nitric oxide. J Clin Invest 1997; 99:1231–7.
31. Pelletier J-P, Martel-Pelletier J, Abramson SB. Osteoarthritis, an inflammatory disease. Potential implication for the selection of new therapeutic targets. Arthritis Rheum 2001;44:1237–47.
32. Raisz LG. Physiology and pathophysiology of bone remodeling. Clin Chem 1999;45:1353–8.
33. Goldring SR, Gravallese EM. Pathogenesis of bone erosions in rheumatoid arthritis. Curr Opin Rheumatol 2000;12:195–9.
34. Leisen JC, Duncan H, Riddle JM, Pitchford WC. The erosive front: a topographic study of the junction between the pannus and the subchondral plate in the macerated rheumatoid metacarpal head. J Rheumatol 1988;15:17–22.
35. Gravallese EM, Harada Y, Wang JT, Gorn AH, Thornhill TS, Goldring SR. Identification of cell types responsible for bone resorption in rheumatoid arthritis and juvenile rheumatoid arthritis. Am J Pathol 1998; 152:943–51.
36. Hummel KM, Petrow PW, Franz JK *et al.* Cysteine proteinase cathepsin K mRNA is expressed in synovium of patients with rheumatoid arthritis and is detected at sites of synovial bone destruction. J Rheumatol 1998; 25:1887–94.
37. Teitelbaum SL. Bone resorption by osteoclasts. Science 2000;289:1504–8.
38. Roux S, Orcel P. Bone loss. Factors that regulate osteoclast differentiation: an update. Arthritis Res 2000;2:451–6.
39. Hofbauer LC, Khosla S, Dunstan CR, Lacey DL, Boyle WJ, Riggs BL. The roles of osteoprotegerin and osteoprotegerin ligand in the paracrine regulation of bone resorption. J Bone Miner Res 2000;15:2–12.
40. Kong YY, Feige U, Sarosi I *et al.* Activated T cells regulate bone loss and joint destruction in adjuvant arthritis through osteoprotegerin ligand. Nature 1999; 402:304–9.
41. Seckinger P, Klein-Nulend J, Alander C, Thompson RC, Dayer JM, Raisz LG. Natural and recombinant human IL-1 receptor antagonists block the effects of IL-1 on bone resorption and prostaglandin production. J Immunol 1990;145:4181–4.
42. Nishihara T, Ohsaki Y, Uedea N, Saito N, Mundy GR. Mouse interleukin-1 receptor antagonist induced by *Actinobacillus actinomycetemcomitans* lipopolysaccharide blocks the effects of interleukin-1 on bone resorption and osteoclast-like cell formation. Infect Immun 1994;62:390–7.
43. Kitazawa R, Kimble RB, Vannice JL, Kung VT, Pacifici R. Interleukin-1 receptor antagonist and tumor necrosis factor binding protein decrease osteoclast formation and bone resorption in ovariectomized mice. J Clin Invest 1994;94:2397–406.
44. Ghivizzani SC, Kang R, Georgescu HI *et al.* Constitutive intra-articular expression of human IL-1 beta following gene transfer to rabbit synovium produces all major pathologies of human rheumatoid arthritis. J Immunol 1997;159:3604–12.
45. van den Berg WB, Joosten LA, Kollias G, van de Loo FA. Role of tumor necrosis factor alpha in experimental arthritis: separate activity of interleukin 1 beta in chronicity and cartilage destruction. Ann Rheum Dis 1999;58(Suppl. 1):I40–8.
46. Horai R, Saijo S, Tanioka H *et al.* Development of chronic inflammatory arthropathy resembling rheumatoid arthritis in interleukin 1 receptor antagonist-deficient mice. J Exp Med 2000;191:313–20.
47. Joosten LA, Helsen MM, Saxne T, van de Loo FA, Heinegård D, van den Berg WB. IL-1 alpha beta blockade prevents cartilage and bone destruction in murine type II collagen-induced arthritis, whereas TNF alpha blockade only ameliorates joint inflammation. J Immunol 1999; 163:5049–55.
48. Bendele A, McAbee T, Sennello G, Frazier J, Chlipala E, McCabe D. Efficacy of sustained blood levels of interelukin-1 receptor antagonist in animal models of arthritis: comparison of efficacy in animal models with human clinical data. Arthritis Rheum 1999;42:498–506.
49. Dawson J, Engelhardt P, Kastelic T, Cheneval D, Mackenzie A, Ramage P. Effects of soluble interleukin-1 type II receptor on rabbit antigen-induced arthritis: clinical, biochemical and histological assessment. Rheumatology 1999;38:401–6.
50. Attur MG, Dave M, Cipolletta C *et al.* Reversal of autocrine and paracrine effects of interleukin 1 (IL-1) in human arthritis by type II IL-1 decoy receptor. Potential for pharmacological intervention. J Biol Chem 2000; 275:40307–15.
51. Makarov SS, Olsen JC, Johnston WN *et al.* Suppression of experimental arthritis by gene transfer of interleukin 1 receptor antagonist cDNA. Proc Natl Acad Sci USA 1996;93:402–6.
52. Muller-Ladner U, Roberts CR, Franklin BN *et al.* Human IL-1Ra gene transfer into human synovial fibroblasts is chondroprotective. J Immunol 1997;158:3492–8.
53. Otani K, Nita I, Macaulay W, Georgescu HI, Robbins PD, Evans CH. Suppression of antigen-induced arthritis in rabbits by *ex vivo* gene therapy. J Immunol 1996;156:3558–62.
54. Pelletier JP, Caron JP, Evans C *et al.* *In vivo* suppression of early experimental osteoarthritis by interleukin-1 receptor antagonist using gene therapy. Arthritis Rheum 1997;40:1012–9.

55. Fernandes J, Tardif G, Martel-Pelletier J *et al*. *In vivo* transfer of interleukin-1 receptor antagonist gene in osteoarthritic rabbit knee joints: prevention of osteoarthritis progression. Am J Pathol 1999;154:1159–69.
56. Bresnihan B, Alvaro-Gracia JM, Cobby M *et al*. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 1998;41:2196–204.
57. Felson DT, Anderson JJ, Boers M *et al*. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The committee on outcome measures in rheumatoid arthritis clinical trials. Arthritis Rheum 1993; 36:729–40.
58. Paulus HE, Egger MJ, Ward JR, Williams HJ, the Cooperative Systematic Studies of Rheumatic Diseases Group. Analysis of improvement in individual rheumatoid arthritis patients treated with disease-modifying antirheumatic drugs, based on findings in patients treated with placebo. Arthritis Rheum 1990;33:477–84.
59. Fries JF, Spitz P, Kraines RG, Holmes HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
60. Jiang Y, Genant HK, Watt I *et al*. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. Arthritis Rheum 2000;43:1001–9.
61. Genant HK, Jiang Y, Peterfy C, Lu Y, Redei J, Countryman PJ. Assessment of rheumatoid arthritis using a modified scoring method on digitized and original radiographs. Arthritis Rheum 1998;41:1583–90.
62. Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. Acta Radiol Diagn 1977;8:481–91.
63. Cohen S, Hurd E, Cush JJ *et al*. Treatment of interleukin-1 receptor antagonist in combination with methotrexate (MTX) in rheumatoid arthritis (RA) patients [abstract]. Arthritis Rheum 1999;42(9 Suppl.):S273.