Blocking the effect of interleukin-1 and tumor necrosis factor in rheumatoid arthritis is well tolerated and effective

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Interleukin (IL)-1 is a primary mediator in the pathophysiology of rheumatoid arthritis. Elevated IL-1 levels have been detected in the synovium of patients with rheumatoid arthritis and such elevated levels have been correlated with disease severity. In animal models, overexpression of IL-1 produces pathology closely resembling rheumatoid arthritis in humans. IL-1 receptor antagonist is an endogenous IL-1 antagonist. Genetically altered mice, designed to be deficient in IL-1 receptor antagonist, spontaneously develop a condition similar to rheumatoid arthritis. Anakinra is a recombinant human IL-1 receptor antagonist approved by the US Food and Drug Administration as a therapy for patients with rheumatoid arthritis. In clinical trials, patients receiving anakinra were more likely to achieve a higher response, as evaluated by the American College of Rheumatology criteria, than patients receiving placebo. Radiologic evaluation indicated a statistically significant slowing of cartilage destruction. Patients treated with a combination of methotrexate and anakinra demonstrated statistically significant improvements in American College of Rheumatology responses and slowing of x-ray progression compared with patients receiving methotrexate alone. Anakinra has been shown to be relatively nontoxic in animal studies and is well tolerated by most patients. The most frequent adverse event is injection site reaction. Anakinra therapy is an effective and well-tolerated treatment for rheumatoid arthritis. In clinical practice, its emerging role is to treat patients who have discontinued therapy with one or more of the agents that block tumor necrosis factor or in patients who have a contraindication to such agents.

Keywords: anakinra, interleukin-1, radiologic evaluation

Rheumatoid arthritis (RA) is a chronic, debilitating, systemic, inflammatory disease characterized by swollen, tender and painful peripheral joints. Active disease results in early and progressive joint destruction leading to significant long-term disability. The most rapid progression of the disease occurs during the first 5 years [1].

Patients with RA experience an increased rate of comorbidities resulting in increased mortality [2]. It has been shown that RA decreases average life expectancy by 3 to 18 years, depending on its severity [3].

The traditional model of RA (joint inflammation causes pain and swelling as well as joint destruction) is being replaced by an emerging model (joint inflammation causes pain and swelling, but synovial hyperplasia causes joint destruction) (**Figure 1**). The treatment strategy should focus on targeting the component of the disease responsible for joint destruction as well as joint inflammation, which leads to significant pain and swelling for RA sufferers. In conjunction with this approach is the development of new disease-modifying antirheumatic drugs (DMARDs) and the introduction of the first generation of biologic response modifiers (BRMs) that target the actual components of the disease responsible for joint destruction.

Although the exact pathogenesis of RA has not been elucidated, strong evidence suggests that the inflammatory mediators, interleukin (IL)-1 and tumor necrosis factor (TNF) are major contributors to the inflammatory and destructive manifestations of RA and have therefore become the targets of new treatment approaches. Three of the four currently available BRMs target TNF (adalimumab [Humira™, Abbott Laboratories) and infliximab [Remicade®, Centocor] doing so as monoclonal antibodies [mAbs], and etanercept [Enbrel®, Amgen] as a fusion protein incorporating soluble TNF receptors), leaving anakinra (Kineret®, Amgen) unique among the BRMs as the only compound that targets IL-1.

Pathophysiology of RA

The pathophysiology of RA is complex. Studies have described the key roles that cellular adhesion molecules, proinflammatory cytokines and metalloproteinases have in mediating the destructive effects of this disease. Cellular adhesion molecules mediate the transmigration of circulating

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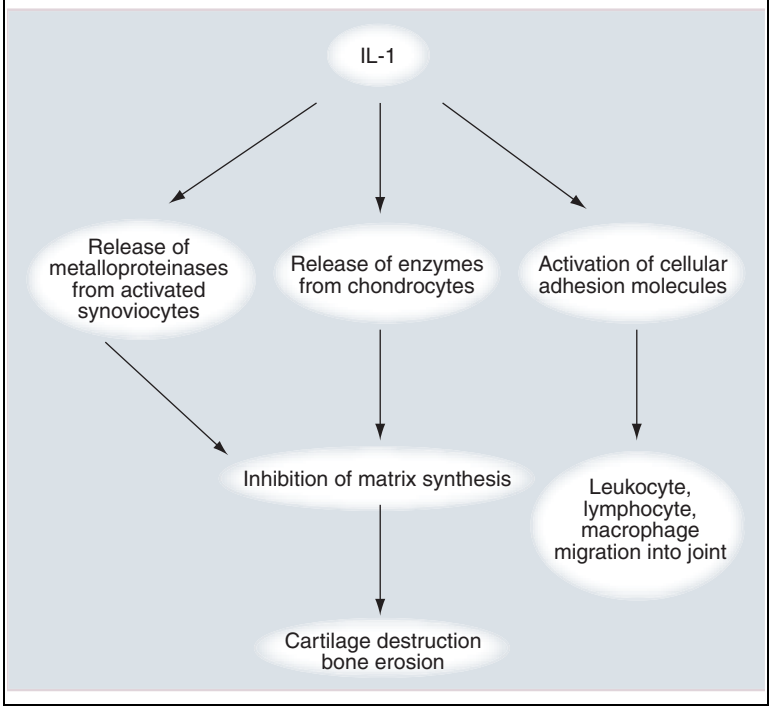
Figure 1. The role of interleukin (IL)-1 in the pathogenesis of cartilage destruction and bone erosion in patients with rheumatoid arthritis.



leukocytes into areas of chronic inflammation as well as the interaction of the cells with the extracellular matrix and resident tissue cells [4]. In the synovial membrane and rheumatoid nodule, the expression of cellular adhesion molecules is regulated by cytokines such as IL-1β and TNF [5].

The release of proinflammatory cytokines accounts for many of the pathologic and clinical manifestations of RA. The rheumatoid synovium is characterized by the presence of IL-1 and TNF. Also detectable are IL-6, interferon (IFN)-α, granulocyte–macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), leukocyte inhibitory factor (LIF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) and transforming growth factor (TGF)β [6]. Nitric oxide and prostaglandin (PG)E_2 are also important mediators of inflammation.

The destruction of bone typically seen in RA is due to increased formation and activation of osteoclasts in the bone. This activation is most likely mediated by osteoprotegerin (OPG) ligand, a transmembrane protein on synoviocytes and activated T-cells. The expression of the OPG ligand is stimulated by proinflammatory cytokines [7–9]. In the Lewis rat model of adjuvant arthritis (AdA) for instance, bone erosion is a major finding. Significant bone preservation was found in association with reduced osteoclast numbers in AdA following the administration of OPG, IL-1 receptor antagonist(Ra), or polyethyleneglycol (PEG)ylated soluble (s)TNF-receptor(R) type I [10]. In addition to the destructive effects mediated by osteoclasts, the synovial fibroblasts in patients with RA may cause erosion of bone by a T-cell-independent pathway [11].

Role of IL-1 in rheumatoid arthritis

The IL-1 gene family consists of IL-1α, IL-1β, and IL-1Ra. IL-1α and β are agonists, and IL-1Ra is a competitive antagonist of IL-1α and β activities. The three genes share significant sequence identity [12,13]. IL-1α and β are synthesized as precursors without leader sequences. The molecular weight of each precursor is 31 kDa – cleaving by cellular proteases results in the mature 17 kDa form. IL-1Ra has a signal peptide and is readily transported out of the cells. Two binding sites are on IL-1 cell surface receptors. All three members of the IL-1 family bind to the first site. IL-1α and β both bind to the second site, however, IL-1Ra does not [14]. The interaction of IL-1α and β with the second binding site is believed to be responsible for inducing destructive effects in target cells.

An imbalance between endogenous IL-1Ra and IL-1 has been suggested as a predisposing factor for the development of RA. Elevated blood levels of IL-1β have been shown in patients with RA [15]. Plasma levels of IL-1β correlated with disease severity. Patients with RA were also shown to have elevated levels of IL-1β compared with IL-1Ra when compared with patients with osteoarthritis or osteomyelitis or patients in normal health [16]. It has been suggested that IL-1Ra may be deficient in patients with RA compared with the amount of IL-1 present [16]. Additional evidence indicating that an imbalance exists between the levels of IL-1 and IL-1Ra in the rheumatoid synovium has been demonstrated in immunohistologic cell culture and animal model studies. In mice with collagen-induced arthritis, elevated levels of IL-1β were detected in the joints and synovium [17]. Levels of IL-1β correlated with the severity of arthritis. During the latter course of the disease, increased production of IL-1Ra was detected in the synovium and a progressive reduction in inflammation was observed. IL-1β and IL-1Ra levels are elevated in the synovial fluid of patients with RA [18,19]. IL-1 is present in 90% of the cells at the cartilage–pannus interface, whereas IL-1Ra is present in less than 10%.

Blocking the effects of IL-1

IL-1Ra is a natural inhibitor of IL-1 and the only known endogenous cytokine receptor antagonist. A recombinant human form of IL-1Ra, anakinra has been developed as a therapeutic approach for the treatment of RA. Anakinra differs from the endogenous form of IL-1Ra only by the presence of an N-terminal methionine. Anakinra behaves similar to the endogenous form – as a pure receptor antagonist. IL-1Ra is produced locally at sites of inflammation. Anakinra is a specific, competitive inhibitor of IL-1 activity that works by blocking the binding of IL-1 to cellular IL-1 surface receptors. *In vitro*, complete inhibition requires a ten- or 100-fold molar excess of IL-1Ra over IL-1 [20]. Anakinra can be administered in doses sufficient to occupy IL-1 receptors and therefore prevent the binding of IL-1. *In vivo* studies employing animal models of RA have shown that administration of anakinra reduces the severity of inflammation. Anakinra reduces mononuclear cell infiltration and IL-1β-mediated pathogenic effects on the synovial membrane of patients with RA [21].

Clinical studies of IL-1 blockade

Treatment with anakinra

In a randomized, double-blind, multicenter monotherapy trial of anakinra, 472 patients with active and severe RA received either placebo or anakinra at doses of 30, 75, or 150 mg/day for 24 weeks [22]. Measurement of American College of Rheumatology (ACR)20 composite index at 24 weeks was the primary efficacy end point. An ACR20 response was observed in 39% of patients receiving 30 mg/day compared with 27% in the placebo group ($p = 0.054$), 34% of patients receiving 75 mg/day compared with placebo ($p = 0.258$) and 43% of patients receiving 150 mg/day compared with placebo ($p = 0.014$).

Clinical responses in the 150 mg/day group were superior to those observed in the other treatment groups and were statistically significant compared with the placebo group with respect to the number of swollen joints ($p = 0.009$), number of tender joints ($p = 0.0009$), Health Assessment Questionnaire (HAQ, $p = 0.0007$), erythrocyte sedimentation rate ($p < 0.0001$) and C-reactive protein ($p = 0.0017$). Clinical responses were observed as early as 2 weeks from the beginning of therapy and the maximal fall in the acute phase response occurred during the first week of treatment [22].

Radiologic evaluation of the hands and wrists showed statistically significant slowing in the rate of progressive joint damage after treatment compared with placebo. The mean Larsen score at 24 weeks in patients treated with anakinra was increased by 3.8, representing a 41% reduction in the rate of radiologic progression compared with placebo ($p = 0.03$) [22]. All three dose groups were similar. An overall reduction of 46% in the erosive joint count was also observed for all dose groups. Only the 30 and 75 mg/day dose groups reached statistical significance compared with placebo. A further analysis of radiologic change using a modified Sharp scoring system that quantifies two aspects of joint damage, articular erosion and joint space narrowing, showed a 58% slowing in the rate

Table 1. Most common adverse events occuring in greater than 5% of patients in the total anakinra group.

Adverse events (%)	MTX + placebo (n = 74)	MTX + anakinra 1.0 mg/kg (n = 59)	MTX + anakinra 2.0 mg/kg (n = 72)	MTX + anakinra all (n = 345)
Injection site reaction	28	64	63	48
Headache	15	34	14	21
Upper respiratory infection	22	24	14	17
Nausea	14	9	8	10
Diarrhea	11	14	8	9
Sinusitis	15	7	10	8
Exacerbation of RA	11	2	7	6
Influenza-like symptoms	5	5	8	6
Abdominal pain	1	7	6	6
Urinary tract infection	5	5	6	5

Adapted from Cohen S et al. Arthritis Rheum. *46, 614–624 (2002).*
MTX: Methotrexate; RA: Rheumatoid arthritis.

Table 2. Distribution of subjects who withdrew prematurely from study across the six randomization arms.

Reason for withdrawal	Placebo (n = 74)	Anakinra mg/kg 0.04 (n = 63)	0.1 (n = 74)	0.4 (n = 77)	1.0 (n =59)	2.0 (n = 72)
Any reason	14 (18.9)	13 (20.6)	12 (16.2)	17 (22.1)	13 (22.0)	19 (26.4)
Adverse event	3 (4.1)	2 (3.2)	1 (1.4)	5 (6.5)	8 (13.6)	11 (15.3)
Protocol violation	1 (1.4)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)
Noncompliance	1 (1.4)	1 (1.6)	2 (2.7)	1 (1.3)	0 (0.0)	1 (1.4)
Lack of efficacy	5 (6.8)	9 (14.3)	7 (19.5)	6 (7.8)	4 (6.8)	4 (5.6)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.9)	0 (0.0)	1 (1.4)
Withdrawal of consent	4 (5.4)	1 (1.6)	2 (2.7)	1 (1.3)	1 (1.7)	2 (2.8)

Number of patients who withdrew with percentages in parentheses. Adapted from Cohen S et al. Arthritis Rheum. *46, 614–624 (2002).*

of progressive joint space narrowing and a 38% slowing in the rate of joint erosion in all anakinra treatment groups [23]. Although subjects exhibited slowing in the rate of radiographic progression, the results of the study correlated less strongly with assessments of disease progression [23].

Effects of anakinra on inflamed synovium

The effects of treatment with anakinra on synovial tissue were evaluated in 12 patients with RA recruited to the monotherapy study [21]. Treatment of RA with anakinra resulted in reduced mononuclear cell infiltration of the synovial membrane. There was a consistent reduction in intimal layer and subintimal layer macrophage and lymphocyte infiltration after treatment with anakinra 150 mg/day. Increased intimal and subintimal cellular infiltration was observed in all patients receiving placebo and variable changes were observed after treatment with anakinra 30 mg/day. At doses of 150 mg/day, down-regulation of E-selectin and vascular cell adhesion molecule (VCAM)-1 was observed.

Treatment with anakinra in combination with methotrexate

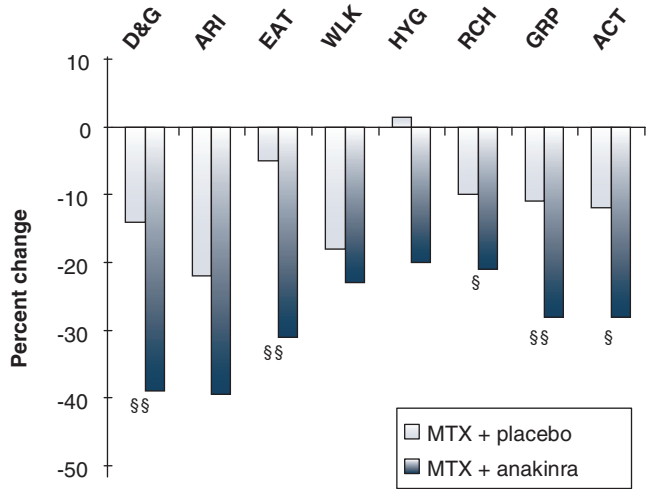
A placebo-controlled, double-blind study in which 419 patients with RA received anakinra in combination with their current maintenance doses of methotrexate (MTX) showed that combination therapy with anakinra and MTX was safe and well tolerated and provided statistically significantly greater clinical benefit than patients continuing on MTX alone [24]. Patients with RA receiving MTX (12.5–25 mg/wk) were randomly assigned to six treatment groups: placebo or anakinra (0.04, 0.01, 0.4, 1.0 or 2.0 mg/kg) to receive daily subcutaneous (s.c.) injection for 24 weeks. Secondary clinical efficacy measurements included the number of swollen joints and tender joints, investigator and patient assessments of disease activity, pain, HAQ, duration of morning stiffness, erythrocyte sedimentation rate and C-reactive protein. The two highest doses of anakinra – 1.0 and 2.0 mg/kg – yielded the strongest treatment effects. The ACR20 response rate in the group receiving anakinra 1.0 mg/kg plus MTX was 46% and 38% in the group receiving

Table 3. Distribution of withdrawals due to adverse events in greater than or equal to two subjects.

Reason for withdrawal	Placebo (n = 14)	Anakinra mg/kg 0.04 (n = 13)	0.1 (n = 74)	0.4 (n = 77)	1.0 (n = 59)	2.0 (n = 72)
Adverse event	3 (4.1)	2 (3.2)	2 (2.7)	5 (6.5)	8 (13.6)	11 (15.3)
Injection site reactions	2 (2.7)	0 (0.0)	0 (0.0)	1 (1.3)	4 (6.8)	7 (9.7)
Hematologic	0 (0.0)	1 (1.6)	1 (1.4)	1 (1.3)	1 (1.7)	1 (1.4)
Respiratory	1 (1.4)	1 (1.6)	0 (0.0)	1 (1.3)	1 (1.7)	0 (0.0)
Body as whole	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.8)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	1 (1.4)

Number of patients who withdrew with percentages in parentheses. Hematologic includes leukopenia or granulocytopenia. Adverse events for which only one person withdrew included reproduction, gastrointestinal, musculoskeletal, skin and appendages and urinary disorders. Adapted from Cohen S et al. Arthritis Rheum. *46, 614–624 (2002).*

Figure 2. Change from baseline to the end of the study (week 24): improvement in patient function observed.



The change in each scale as a percentage of baseline value presents a similar picture. By week 24, patients on anakinra experienced improvements of at least 20% for all scales (five of the eight were statistically significantly superior to MTX + placebo). Patients on MTX + placebo experienced a 20% improvement for only one scale (arising).
ACT: Activities (errands and chores); ARI: Arising; D&G: Dressing and grooming; EAT: Eating; GRP: Grip; HYG: Hygiene; MTX: Methotrexate; RCH: Reach; WLK: Walking. §$p < 0.05$; §§$p < 0.01$.
Adapted from Cohen S *et al. J. Rheumatol.* 30, 225–231 (2003).

2.0 mg/kg plus MTX. When compared with the MTX and placebo group's ACR20 response rate of 19%, the anakinra 1.0 and 2.0 mg/kg groups were clinically and statistically better ($p = 0.001$ and $p = 0.007$, respectively). **Table 1** shows the overall incidence of adverse events. **Table 2** shows withdrawals due to adverse events and lack of efficacy and **Table 3** shows the incidence of adverse events in those withdrawals. **Figures 2 & 3** show the improvement in patient function observed [25].

In a double-blind, placebo-controlled trial enrolling 506 patients with active RA despite current treatment with MTX 10 to 25 mg/wk, patients were randomly assigned 1:1 to anakinra 100 mg s.c. daily or placebo. A significantly greater number of patients receiving anakinra in combination with MTX achieved ACR20 (38 vs 22%; $p < 0.001$), ACR50 (17 vs 8%; $p < 0.01$) and ACR70 (6 vs 2%; $p < 0.05$) responses after 24 weeks compared with patients receiving MTX alone [26]. In the combination study, the overall incidence of infectious episodes was reported more frequently in anakinra-treated patients (33%) than in those treated with placebo (26%) [26]. However, the incidence of serious infections was the same for both treatment groups (0.8%) [26]. At the first study assessment (4 weeks), the proportion of patients with an ACR20 response was twice as high with anakinra as with placebo ($p < 0.005$).

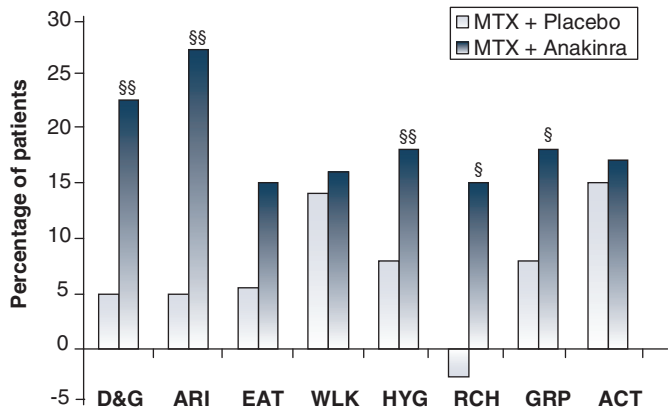
Safety & tolerability of anakinra

Intravenous injection of anakinra in healthy volunteers at doses 1 million-fold greater than the concentration of IL-1α and β has provided evidence of anakinra's safety [25]. Due to the fact that anakinra functions as a pure receptor antagonist, no agonistic properties are detectable even at these high doses [25]. No changes in creatinine clearance rates or liver enzyme levels were observed in healthy, normal volunteers receiving anakinra therapy [22]. In the monotherapy study, injection site reaction was the most frequent adverse event occurring in 25% of patients receiving placebo and in 50, 73 and 81% of patients receiving anakinra at 30, 75, and 150 mg/day, respectively [22]. These reactions were usually mild and resolved within 2 to 3 weeks. Premature withdrawal from the study occurred in all study groups, with the highest percentage (32%) of patients withdrawing from the placebo group, followed by 28, 24 and 22% of patients receiving anakinra at 150, 30, and 75 mg/day, respectively. No increase in the prevalence of anti-IL-1Ra antibodies was detected after treatment with anakinra [22]. In the combination study, the overall incidences of infectious episodes were reported more frequently in anakinra-treated patients (33%) than those treated with placebo (26%) [26]. However, the incidence of serious infections was the same for both treatment groups (0.8%) [26].

In the combination anakinra–MTX study, 16 to 26% of anakinra-treated subjects withdrew prematurely. Lack of efficacy (6–14%) and adverse events (1–15%) were the most common reasons for withdrawal. The withdrawal rate for lack of efficacy was greatest in the anakinra 0.04 mg/kg group (14%). Most withdrawals in the anakinra 1.0 and 2.0 mg/kg groups (14–15%, respectively) were due to injection site reactions [24].

Anakinra was generally well tolerated. As in the monotherapy study, the most frequent adverse event in the MTX combination study was also dose-related injection site reaction. Most of these reactions tended to diminish with repeated doses. Signs and symptoms of injection site reactions included pain, erythema, pruritus, and rash. Headache, reported in 15% of placebo-treated subjects and 14 to

Figure 3. Change from baseline to the end of the study (week 24) in the percentage of patients who reported no impairment in function.



Note that an increase in this value implies that more patients are attaining this higher functioning state. Averaging across the scales, 19% of patients on anakinra achieved a state of no impairment in function versus 7% of patients on placebo.
ACT: Activities (errands and chores); ARI: Arising; D&G: Dressing and grooming; EAT: Eating; GRP: Grip; HYG: Hygiene; MTX: Methotrexate; RCH: Reach; WLK: Walking. $^{\S}p < 0.05$; $^{\S\S}p < 0.01$.
Adapted from Cohen S *et al. J. Rheumatol.* 30, 225–231 (2003).

34% of anakinra-treated subjects, was the second most frequently reported adverse event. There were no reports of serious infections during the study [24]. Of the patients receiving active treatment, 6% reported abdominal pain, compared with 1% of placebo-treated patients. Arthralgia and worsening of RA were observed more often in the placebo group (7%) than in the anakinra group.

Premature withdrawal from the study due to leukopenia occurred in five patients. Four of the five subjects developed a white blood cell (WBC) count of less than or equal to 3.0×10^9/L (range, 2.5×10^9 to 3.0×10^9/L), the limit specified in the study protocol for withdrawal. After discontinuation of anakinra treatment, WBC counts returned to normal. These brief episodes of leukopenia did not involve fever, infection, or sepsis. No dose relationship was observed with these occurrences of leukopenia. Two new malignancies were diagnosed during the study, one in a placebo-treated patient and one in an anakinra-treated patient (2.0 mg/kg) with a history of ovarian cyst, who developed breast cancer. Both subjects were withdrawn from the study; neither malignancy was considered to be related to the study drug. No deaths occurred during this study [24].

We recently evaluated the safety of anakinra in a large (n = 1414) double-blind, placebo-controlled study designed to reflect a patient population typically seen in clinical practice – patients with a broad range of RA activity, a wide range of comorbidities and various combinations of concomitant RA therapies [27]. Patients were allowed to use nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids and DMARDs, with the exception of TNF inhibitors. Patients were randomly assigned to anakinra 100 mg (n = 1116) or placebo (n = 283). After 6 months the rates of serious adverse events were similar: 7.7% in the anakinra group versus 7.8% in the placebo. Serious infections were more frequent in the anakinra group (2.1%) than in the placebo group (0.4%), however, 17 of the 23 anakinra patients with serious infections resumed anakinra therapy after the infection resolved. No opportunistic infections were reported. Rates of premature study withdrawal were similar (anakinra, 21.6%; placebo, 18.7%). Injection site reactions were the most commonly reported adverse event (anakinra, 72.6%; placebo, 32.9%). Most were transient and of mild or moderate severity. We recently reported preliminary data from a 36-month, open-label continuation of this study in which 1399 patients chose to participate [28]. These 36-month data, which provide long-term safety data for 2273 patient-years of exposure to anakinra, have revealed no new safety issues other than an increased risk of lymphoma similar to patients with RA not treated with BRMs.

Clinical trials of anti-TNF agents

Patients with RA who are candidates for anakinra have most often had a previous treatment trial with one of the anti-TNF agents or have contraindications for use of these agents. Three such therapies are available in the USA; etanercept, infliximab, and adalimumab. Etanercept is approved for monotherapy or in combination with MTX [29]. The recommended dose for adults with RA is 25 mg adminstered as a s.c. injection twice a week or 50 mg once weekly. For treating juvenile RA in patients aged 4 to 17 years, the recommended twice-weekly dose is 0.4 mg/kg, to a maximum of 25 mg per dose or a once-weekly dose of 0.8 mg/kg, to a maximum of 50 mg per dose. Being chimeric (mouse–human), infliximab has been approved for use in combination with MTX, which may be necessary to manage the formation of human antichimeric antibodies

when infliximab is used in low doses. The maintenance dose of infliximab for treatment of RA is 3 mg/kg every 8 weeks administered by intravenous infusion, following the initial infusion and subsequent doses 2 and 6 weeks thereafter, all at the same rate [30]. The dose can be titrated to as high as 10 mg/kg and can be administered as frequently as every 4 weeks. Adalimumab, a fully human mAb, is indicated for use as RA monotherapy or in combination with MTX or other DMARDs [31]. It is administered s.c. in a 40 mg dose every other week or 40 mg weekly.

The efficacy of etanercept 25 mg twice weekly was confirmed in a 6-month study in which 234 patients who had inadequately responded to one to four DMARDs were randomly assigned to etanercept 10 or 25 mg or placebo twice weekly [32]. After 6 months, the ACR20 and ACR50 response rates were greatest in the etanercept 25 mg group and significantly greater than those of placebo ($p < 0.001$ and $p < 0.01$, respectively). In addition, the mean tender joint count was reduced by 56% in the etanercept 25 mg group, compared with a 6% reduction in the placebo group ($p < 0.05$) and minimal disease (0–5 tender or swollen joints) was achieved by 17% of the etanercept 25 mg group versus 3% of placebo ($p < 0.005$).

Etanercept has also been studied in a population with early RA (n = 632) [33,34]. During the first 6 months, patients receiving etanercept 25 mg generally had statistically significantly greater ACR20, 50 and 70 response rates than patients receiving MTX, however, during months 7 to 12, the difference was not statistically significant. After 12 months, an ACR20 response was achieved by 72% of the etanercept 25 mg group and 65% of the MTX group ($p = 0.16$). As judged by Sharp scores, 72% of the etanercept 25 mg group had no increase in the erosion score, compared with 60% of patients receiving MTX ($p = 0.007$). After completing the blinded portion of the study, 512 patients continued receiving their initial therapy in a 12-month open-label extension [34]. After 24 months, 72% of patients in the etanercept 25 mg group achieved an ACR20 response rate, compared with 59% of patients in the MTX group ($p = 0.005$). After 24 months, etanercept 25 mg was significantly more effective than MTX in inhibiting radiographic progression of RA.

The Trial of Etanercept and MTX with Radiographic Patient Outcomes (TEMPO) determined that the combination of MTX and etanercept is more effective than MTX alone in patients with established RA [35,36]. At week 52 in this multicenter, randomized, double-blind study comparing etanercept and MTX (alone and in combination), a mean of 85% of patients treated with combination therapy achieved ACR20 compared with 75 and 76% in the MTX and etanercept groups, respectively ($p = 0.0091$ for combination vs MTX; $p = 0.0151$ for combination vs etanercept). ACR50 and ACR70 were also assessed at week 52. In the combination group, 69% achieved ACR50 compared with 43 and 48% in the MTX and etanercept groups, respectively ($p < 0.0001$ for combination vs MTX; $p < 0.0001$ for combination vs etanercept). Combination therapy also resulted in mean negative radiographic progression scores as evidenced by the mean total Sharp scores. The mean total Sharp score for combination therapy was -0.54 (confidence interval [CI]: -1.00 to -0.07), as compared with 2.80 (CI: 1.08 to 4.51) and 0.52 (CI: -0.10 to 1.15) for MTX and etanercept, respectively. Clinical remission rates at 52 weeks, defined as a disease activity score of less than 1.6, were 35, 13 and 16% for the combination, MTX and etanercept groups, respectively ($p < 0.0001$ for combination vs. MTX; $p < 0.0001$ for combination vs etanercept; $p = 0.5031$ for etanercept vs MTX) [36].

The safety and efficacy of infliximab was assessed in the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) trial, which enrolled 428 patients whose RA was inadequately controlled by MTX [37,38]. Patients were randomly assigned to placebo, infliximab 3 mg/kg every 4 or 8 weeks or infliximab 10 mg/kg every 4 or 8 weeks, following initial infusions at weeks 0, 2, and 6. After 30 weeks, ACR20 response rates were 53 and 50% in the groups receiving 3 mg/kg every 4 or 8 weeks respectively and 58 and 52% in the groups receiving 10 mg/kg every 4 or 8 weeks, respectively, compared with an ACR20 response rate of 20% in the group receiving placebo plus MTX ($p < 0.001$ for each infliximab group vs placebo) [37]. The ACR50 response rates were 29 and 27% in the groups receiving 3 mg/kg every 4 or 8 weeks, respectively and 26 and 31% in the groups receiving 10 mg/kg every 4 or 8 weeks, respectively, compared with an ACR50 response rate of 5% in the group receiving placebo plus MTX ($p < 0.001$).

These results were sustained after 54 weeks [38]. Among patients receiving infliximab 3 mg/kg

every 4 or 8 weeks, the ACR20 response rates were 48 and 42%, respectively; 10 mg/kg every 4 or 8 weeks, 59% in each group compared with 17% in the placebo plus MTX group. ACR50 response rates were 34 and 21% in the groups receiving infliximab 3 mg/kg every 4 or 8 weeks, respectively; 10 mg/kg every 4 or 8 weeks, 38 and 39%, respectively, compared with 8% in the placebo group. Patients receiving infliximab had no radiographic evidence of progression of joint disease, as demonstrated by the mean change in radiographic scores (7.0 vs 0.6; $p < 0.001$) in the MTX and infliximab groups, respectively.

The Active Controlled Study of Patients Receiving Infliximab for the Treatment of RA (ASPIRE) trial evaluated the effectiveness of MTX versus combination therapy with infliximab and MTX for 52 weeks [39]. Combination therapy resulted in greater improvement in ACR response and a greater retardation of radiographic progression as determined by the van der Heijde-modified Sharp score ($p < 0.05$) [39].

As monotherapy, adalimumab was evaluated in 544 patients who had failed treatment with at least one DMARD [31]. After 26 weeks, patients receiving adalimumab 40 mg every other week had fewer tender joints (16 vs 26); fewer swollen joints (10 vs 16); better global assessments by physicians (3.7 vs 6.1) and patients (4.5 vs 6.3), on a visual analog scale of 0–10; less pain (4.1 vs 6.1, also on a visual analog scale of 0–10); a lower HAQ disability index (1.5 vs 1.9) and less C-reactive protein (1.8 vs 4.3 mg/dL). All comparisons were statistically significant.

The efficacy of adalimumab in combination with MTX was demonstrated in a trial enrolling 271 patients who had failed therapy with one to four DMARDs and whose response to MTX was inadequate [40]. After 24 weeks, the ACR20, 50, and 70 response rates were greatest in the adalimumab 40 mg group (67, 55 and 27%, respectively) and were statistically significantly greater than the placebo response rates (14, 8 and 5%, respectively) ($p < 0.01$). In another trial enrolling 619 patients who had responded inadequately to MTX, patients receiving adalimumab 40 mg every other week plus MTX ($n = 207$) had ACR, 50 and 70 response rates of 63, 39 and 21%, respectively, after 24 weeks, compared with response rates of 30, 10 and 3%, respectively, among patients receiving MTX plus placebo [31]. After 52 weeks, the ACR response rates in the adalimumab 40 mg group were sustained, at 59, 42 and 23%, respectively (52-week placebo response rates of 24, 10 and 5%, respectively).

A multicenter, 52-week, double-blind, placebo-controlled study in 619 patients with active RA evaluated the ability of adalimumab to inhibit the progression of structural joint damage, reduce the signs and symptoms and improve physical function in patients with active RA receiving concomitant MTX therapy [41]. At week 52 there was less radiographic progression as measured by modified total Sharp score in patients receiving adalimumab as compared with placebo ($p \leq 0.001$). At week 52, ACR 20 responses were achieved by 57% of adalimumab treated patients versus 24% in those receiving placebo ($p \leq 0.001$).

Designed as a study of what clinicians may do in a more 'real world' setting, the BeSt trial included 508 patients with early rheumatoid arthritis and no DMARD therapy. It compared the effects of multiple treatment regimens with respect to 1 year radiographic and HAQ results. Combination therapy as an initial treatment regimen resulted in a significantly less radiographic progression than sequential monotherapy or step-up therapy and a more rapid decline in HAQ scores. Irrespective of the randomized treatment assignment, 44% of all patients stated a preference for treatment for the newest intravenous drug for RA, as compared with a regimen with steroids [42].

Tuberculosis (TB) and other opportunistic infections have been reported with the anti-TNF agents. At a March 2003 meeting of the US Food and Drug Adminsitration (FDA) Arthritis Advisory Committee, it was stated that 172 cumulative cases of TB had been reported in the USA in patients receiving infliximab during the period between August 23, 1998 (the day before infliximab was first approved for use in the USA for Crohn's disease) and December 31, 2002 [43]. In this same report, 38 cases of TB were reported in the USA in patients receiving etanercept [43]. In clinical trials, adalimumab has also been associated with 13 cases of TB at all doses, but increasingly at the higher doses, which implies a dose–response effect.

The critical importance of proper TB screening and management in patients with RA who are to undergo treatment with a TNF inhibitor is underscored by evidence that the guidelines and recommendations have greatly reduced the incidence of TNF inhibitor-related TB in Spain where the estimated incidence of TB associated

with infliximab was 1893 per 100,000 and 1113 per 100,000 in 2000 and 2001, respectively. On the other hand, during the first 5 months of 2002, after official guidelines were established for the prevention of TB in patients treated with biologics, only one new case was registered [44].

The infliximab and adalimumab product inserts both bear 'black box' warnings stating that cases of TB (frequently disseminated or extrapulmonary at clinical presentation) have been seen in patients treated with either agent [30,31]. The labels advise evaluating patients for latent TB infection with a tuberculin skin test and treating any latent TB infection before treatment with adalimumab or infliximab. The etanercept product label warns that rare cases of TB have been observed among patients receiving etanercept [29].

Postmarketing reports indicate that *Listeria* and *Histoplasma* infections may be a complication of treatment with anti-TNF agents, particularly infliximab [45,46]. In clinical trials and postmarketing experience, rare cases of opportunistic infections have been observed with anakinra (and included fungal, mycobacterial and bacterial pathogens) [47]. Rarely, anti-TNF agents have been associated with optic neuritis, demyelinating disorders, antibody formation and increased risk of lymphomas [48–50].

Immunosuppressed and immunodeficient patients are at an increased risk of developing lymphoproliferative disorders, especially non-Hodgkin's lymphoma and patients with RA face this excess risk because of dysregulated immune function inherent to the disease. Moreover, the immunosuppressive effects of many agents used to treat RA may also contribute to the development of lymphoproliferative malignancies. A review of the FDA MedWatch surveillance system identified 26 cases of lymphoproliferative disorders following treatment with either etanercept (18) or infliximab (8) as of December 2000. The majority of these cases (81%) were non-Hodgkin's lymphomas, suggesting that the use of etanercept and/or infliximab in patients with RA may be a cause for concern regarding lymphoma [48]. Similarly, the IL-1 receptor antagonist, anakinra, has been associated with an increased risk of lymphomas. In clinical trials involving 5300 patients taking anakinra, eight lymphomas were observed, equaling a rate of approximately 0.12 cases/100 patient years. This rate is 3.6 times higher than the lymphoma incidence expected in the general population [47]. However, the standardized incidence ratio (SIR) for lymphoma in patients with RA is similar among those taking a BRM and those not taking one of these drugs [51]. Thus, a definitive conclusion concerning an increased risk of lymphoma among patients taking a BRM cannot be drawn at this time.

An increased risk of the onset or worsening of congestive heart failure (CHF) has also been linked to anti-TNF therapies. Based on data from animal models and human disease, TNF may contribute to the pathogenesis of CHF [43]. Anti-TNF agents should be used with caution in patients with CHF according to the product labeling.

The role of anakinra amidst the other biologic response modifiers

Although the idea of simultaneously inhibiting IL-1 and TNF with complementary BRMs seems promising on theoretical grounds, the combination of anakinra plus etanercept provided no additional advantage over etanercept alone in a recent double-blind, active-controlled study [52]. Patients were randomly assigned to etanercept 25 mg twice weekly (n = 80), etanercept 25 mg once weekly plus anakinra 100 mg daily (n = 81), or etanercept 25 mg twice weekly plus anakinra 100 mg s.c. daily (n = 81). All patients were on stable background therapy with MTX 10 to 25 mg/wk and stable doses of NSAIDs and corticosteroids. No statistically significant difference was observed between the ACR50 response rate of 41% in the etanercept-only group and the 31% ACR50 response rate of patients receiving twice-weekly etanercept plus anakinra ($p = 0.914$). The incidence of serious infections for etanercept-only and etanercept combination therapy were 0 versus 3.7 to 7.4% respectively. Similar results were observed in a smaller study of 58 patients. Of these, 28 had episodes of infection, of which four (two episodes of cellulitis and two of pneumonia) required hospitalization; all patients recovered with antibiotic treatment [53]. The anakinra package insert therefore alerts users to the lack of efficacy and increased risk of infection from combination therapy with anakinra and etanercept, warning physicians to weigh the risks and benefits and to monitor patients carefully if they decide to begin concomitant therapy with anakinra and etanercept [47].

Thus, it seems prudent to use anakinra sequentially rather than concurrently with

etanercept and perhaps the other anti-TNF agents, as the package insert suggests. Indeed, the emerging pattern in clinical practice is to reserve anakinra for treating patients who have discontinued an anti-TNF agent, owing to lack of effectiveness or intolerance [54]. It is estimated that by the end of 2003, approximately 55,000 patients will have discontinued one or more anti-TNF agents.

In a prospective study (Rheumatoid Arthritis DMARD Intervention and Utilization Study [RADIUS 1]), 52% (186/358) of patients who began anakinra therapy previously were on an anti-TNF agent (etanercept, 72%; infliximab, 54%; both, 25%) [55]. Of those, 70% whose RA was of long duration (mean years, 10.7) and considerable severity (moderate, 48%; severe, 49%), continued on anakinra therapy for 6 months, which implies satisfactory efficacy. These preliminary data support the use of anakinra to treat the majority of patients who were previously but inadequately treated with an anti-TNF agent. The Kineret® Response Assessment Initiative (KREATIVE protocol) assessed the response rate, time-to-response, efficacy and safety during 52 weeks of therapy with anakinra in RA patients in Germany [56]. Patients in this trial had an average duration of RA of 13 years. In addition, 73% received concomitant MTX therapy and 44% had been treated previously with an anti-TNF agent. After 3 months of therapy, 66% of patients showed good or moderate response to anakinra therapy (based on European League Against Rheumatism [EULAR] criteria). As demonstrated in the previous trial, these data suggest that anakinra may be effective in patients who have been inadequately treated with an anti-TNF agent. However, RA patients treated with TNF blockers may demonstrate a heterogeneous response to therapy, raising the possibility that a different cytokine such as IL-1 may predominate in certain cases. Buch and colleagues identified 26 patients (aged between 26–76 years) with RA who failed a TNF-α blocker and were then treated with anakinra (100 mg/kg s.c.) for 12 weeks. After 3 months of anakinra therapy, only two (8%) patients achieved an ACR20 response and none achieved an ACR50 or 70 response. In addition, a rise in the mean C-reactive protein level and an increase in the mean swollen joint count were noted. These data may underscore that proinflammatory cytokines other than TNF and IL-1 may be involved in the pathogenesis of RA [57].

Expert opinion

The pathogenesis of RA is complex. Anakinra is unique among the BRMs in targeting IL-1, which has been shown to play a vital role in the pathogenesis of synovial inflammation and more importantly of bone and cartilage destruction. The inhibition of progressive bone erosion is one of the most exciting and clinically promising features of therapy with the new BRMs. In clinical trials, anakinra therapy has been a safe, well tolerated and efficacious treatment for patients with RA. Patients have reported significant improvement in such clinical measures as pain, swelling of joints and duration of morning stiffness. Importantly, patients who received anakinra had significant decreases in progressive bone erosion, as has been observed in patients receiving etanercept alone [33,34], or infliximab in combination with MTX [38].

Outlook

There are a number of medications available for the treatment of rheumatoid arthritis, including anakinra, an IL-1 antagonist, and the TNF-inhibitors etanercept, infliximab, and adalimumab. The biologic response modifiers offer new opportunities to treat and halt the progression of rheumatoid arthritis. Clinical trials continue to investigate the benefits and safety profiles of these novel therapies.

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Highlights

- Rheumatoid arthritis (RA) is a disease that affects a significant percentage of the population, is very debilitating and leads to significant long-term disability.
- Interleukin (IL)-1 is a primary mediator in the pathophysiology of RA.
- Inhibition of progressive bone erosions is one of the most clinically promising features of therapy with biologic response modifiers.
- In clinical practice, the emerging role of anakinra is to treat patients who have discontinued therapy with one or more of the tumor necrosis factor-inhibitors or in patients who have a contraindication to these agents.

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