Preventing Joint Damage as the Best Measure of Biologic Drug Therapy

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ABSTRACT. Joint damage occurs progressively in patients with rheumatoid arthritis (RA), leading to functional decline and disability. The proinflammatory cytokines interleukin 1 (IL-1) and tumor necrosis factor-α (TNF-α) are thought to play a key role in promoting cartilage and bone erosion in the rheumatoid joint. In randomized clinical trials, inhibitors of these cytokines significantly slowed the rate of progressive joint damage as assessed by radiographic techniques. The IL-1 receptor antagonist anakinra significantly reduced erosions, joint space narrowing, and total joint damage when a modified Sharp score was used to evaluate serial hand radiographs. The maximum benefit of anakinra on joint space narrowing was achieved within the first 24 weeks and was maintained during continued treatment, whereas the slowing of erosions by anakinra increased with continued treatment beyond 24 weeks. In terms of TNF-α inhibition, infliximab significantly reduced joint damage in patients with long-standing RA, when used in combination with methotrexate (MTX), whereas etanercept significantly reduced erosions relative to MTX in patients with early stage disease. Comparisons among the cytokine inhibitors are made problematic by differences in the designs, patient populations, and outcome measures of these trials. Nevertheless, these studies demonstrate that IL-1 or TNF-α inhibition effectively suppresses the pathophysiological mechanisms associated with cartilage degradation and bone erosion, resulting in a slowing of further radiographic progression. (J Rheumatol 2002;29 Suppl 65:39–43)

Key Indexing Terms:
ANAKINRA JOINT EROSION CYTOKINES RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by progressive joint damage leading to functional decline and disability[1,2]. When followed longitudinally, joint damage is evident in early RA, and it increases at a constant rate for at least 10 to 20 years. In a study of 256 patients with RA, serial hand radiographs showed constant radiographic progression, with changes in total Sharp score averaging 4.5 per year[3]. Radiographic progression was closely correlated with the level of inflammation as reflected by the erythrocyte sedimentation rate (ESR). The association between radiographic progression and ESR increased over time, with the highest correlation observed after 10 years of disease. Other clinical variables, including grip strength, rheumatoid factor positivity, and tender joint count, also independently predicted radiographic progression.

The mechanisms responsible for causing joint damage and functional impairment in RA are complex and involve many proinflammatory mediators and degradative enzymes. The proinflammatory cytokines interleukin 1 (IL-1) and tumor necrosis factor-α (TNF-α) are believed to play an important role in the pathogenesis of RA[4,5]. Immunohistochemical analyses of RA synovial biopsies show that these cytokines are expressed in abundant amounts[6]. In specimens from patients with early RA, cells expressing IL-1α and IL-1ß occupied a mean of 14.8% and 14.9% of the cartilage-pannus junction region, respectively, as compared with 6.7% for cells expressing TNF-α. Cells expressing TNF-α tended to cluster in areas with high levels of macroscopic inflammation. Importantly, expression of these cytokines varied considerably among synovial specimens, with up to 59% of the tissue occupied by cells producing IL-1ß and up to 12% of the tissue occupied by cells expressing TNF-α. Conversely, some specimens showed low levels of IL-1 and TNF-α production. Importantly, IL-1 and TNF-α production did not appear to be related. Treatment with the anti-TNF-α monoclonal antibody infliximab significantly reduced TNF-α synthesis in these synovial specimens, whereas the effects on IL-1α and IL-1ß production were inconsistent[7].

The expression of IL-1 and TNF-α by synovial tissue is consistent with a number of consequences that are recognized clinically in patients with RA. These cytokines contribute to mechanisms that result in synovial inflammation and cartilage and bone degradation (Figure 1)[8]. They upregulate expression of cell adhesion molecules, chemokines, prostanoids, and neuropeptides, which promote cell migration and enhance endothelial perme-

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Supported by an unrestricted educational grant from Amgen, Inc.

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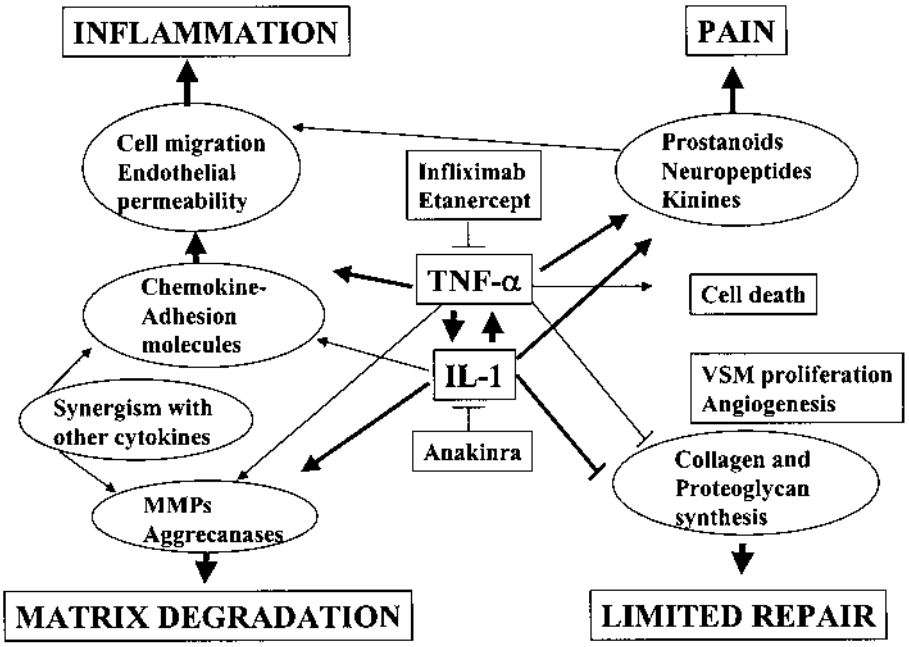

Figure 1. Central role of IL-1 and TNF-α in the pathogenesis of RA. VSM: vascular smooth muscle. From Dayer JM, Bresnihan BI[16], with permission.

ability leading to synovial inflammation. The production of prostanoids and neuropeptides is also responsible for causing pain in affected joints. The cytokines also induce expression of matrix metalloproteinases and aggrecanases that degrade the cartilage matrix, and inhibit collagen and proteoglycan synthesis, thus limiting repair of damaged cartilage. In addition, they contribute to the differentiation and activation of osteoclasts, leading to resorption of bone matrix. The availability of cytokine inhibitors — the TNF-α blockers infliximab and etanercept and the IL-1 receptor antagonist anakinra — now makes it possible to direct therapy at mechanisms believed to be responsible for synovial inflammation and matrix degradation in RA.

EFFECT OF ANAKINRA ON JOINT DAMAGE

The influence of anakinra on clinical variables and radiographic progression was demonstrated in a randomized controlled trial conducted at 41 centers in 11 European countries[9]. Patients with active RA discontinued previous disease modifying antirheumatic drugs (DMARD), and then were randomly assigned to receive anakinra 30, 75, or 150 mg or placebo once daily for 24 weeks by subcutaneous injection. At the end of the placebo controlled phase, patients were eligible to continue treatment during a 24 week double blind extension phase. Patients in the placebo group were randomized to one of the 3 anakinra treatment arms, whereas those taking anakinra continued the same dose.

Serial hand radiographs were taken at baseline and after 24 and 48 weeks of treatment[10]. Joint damage was scored by the Genant modification of the Sharp method[11]. Briefly, erosions were scored on a scale of 0 to 3.5 in 14 joints of each hand, whereas joint space narrowing was scored on a scale of 0 to 4 in 13 joints of each hand. The maximal erosion and joint space narrowing scores were 98 and 104, respectively, and therefore the maximum Sharp score was 202.

A total of 472 patients were randomized to treatment, including 351 patients to one of the 3 doses of anakinra and 121 patients to placebo (Table 1). Overall, the mean age was 53 years, and most patients (75%) were female. Patients had relatively severe disease at enrollment, with 74% having evidence of erosive disease and 69% positive for rheuma-

Table 1. Demographic and disease characteristics of patients in anakinra study. Values are mean (SD) or percentages.

	Placebo, n = 121	Anakinra, n = 351
Age, yrs	52.2 (11.9)	53.4 (13.2)
Female, %	70.2	76.6
Presence of erosive disease, %	74.4	73.2
Rheumatoid factor positive, %	69.4	69.5
Swollen joint count, 0–66	25.6 (10.3)	26.3 (9.8)
HAQ, 0–3	1.5 (0.6)	1.6 (0.7)
RA duration yrs	3.7 (2.4)	4.1 (2.4)
C-reactive protein, mg/dl	4.3 (4.3)	4.1 (3.8)
ESR, mm/h	47.1 (30.0)	50.3 (29.0)
Sharp total score, 0–202	27.1 (28.1)	27.3 (26.3)
Sharp JSN score, 0–104	11.7 (14.2)	12.5 (13.7)
Sharp erosion score, 0–98	15.4 (14.7)	14.8 (13.6)

HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; JSN: joint space narrowing.

toid factor. The swollen joint count averaged 26, and the Health Assessment Questionnaire (HAQ) score averaged 1.6. Patients were relatively early in their course of disease, with a mean duration of 4 years since symptom onset. The modified total Sharp score in hand radiographs averaged 27, and therefore the annual rate of change in Sharp score was in excess of 6.

During the 24 week double blind phase, the increase in modified total Sharp score was significantly lower with anakinra than placebo (1.9 vs 3.5; $p = 0.0004$). The effect of anakinra was also evident in the joint space narrowing (0.7 vs 1.6; $p = 0.0003$) and erosion (1.2 vs 1.9; $p = 0.0097$) scores[10]. Moreover, patients receiving anakinra were significantly more likely to show apparent arrest of disease as defined by zero or negative changes from baseline in total Sharp score (33% vs 20%; $p = 0.005$) or in joint space narrowing (44% vs 26%; $p < 0.001$) or erosion (38% vs 26%; $p = 0.009$) scores.

The reduction in joint damage during anakinra therapy was accompanied by significant reductions in many clinical signs and symptoms of active RA[9]. Anakinra significantly reduced tender joint counts ($p = 0.005$), pain ($p = 0.003$), HAQ score ($p = 0.001$), duration of morning stiffness ($p = 0.007$), ESR ($p < 0.0001$), and C-reactive protein ($p = 0.0002$) as compared with placebo. In addition, anakinra provided significant improvements in the investigator ($p = 0.002$) and patient ($p = 0.017$) assessments of disease activity. Overall, the percentage of patients achieving American College of Rheumatology (ACR) 20% response criteria was significantly higher with anakinra (39% vs 27%; $p = 0.02$).

Radiographic data at 12 months provide further evidence of the benefit of anakinra on joint damage. The rate of radiographic progression during the extension study slowed in patients switched from placebo to anakinra, and it also slowed in those who continued anakinra. In the group of 58 patients treated initially with placebo and then switched to anakinra, the mean (median) change in total Sharp score during placebo treatment of 3.7 (2.2) declined significantly during the subsequent interval of anakinra treatment to 1.6 (0.1) ($p < 0.001$) (Figure 2A). Similarly, in the group of 178 patients treated with anakinra for the entire 12 month period, the mean (median) change in total Sharp score declined significantly from 2.4 (0.6) during the first 6 month period to 1.3 (< 0.1) during the second 6 month interval ($p < 0.001$). Thus, the benefit of anakinra in slowing radiographic progression appeared to be cumulative during continued treatment.

The change in joint space narrowing and erosion scores both declined significantly when patients were switched from placebo to anakinra (both $p < 0.001$) (Figure 2B and 2C). In comparison, patients treated with anakinra for 12 months continued to show the same level of reduced joint space narrowing during the extension phase, but importantly, erosions slowed even further during the extension phase relative to the initial 24 week treatment period ($p < 0.001$). Thus, the maximum therapeutic benefit on joint space narrowing occurred during the first 6 months of treatment, and was maintained during continued treatment, but the maximum benefit on erosions occurred during the second 6 months of treatment.

COMPARISON OF ANAKINRA AND TNF-α BLOCKERS

The TNF-α blockers etanercept and infliximab have also been shown to slow radiographic progression in patients with active RA[12,13]. However, comparisons between anakinra and the TNF-α blockers are problematic because the studies differed in terms of study designs, patient populations, and outcome measures. As shown in Table 2 the mean RA duration of patients in the studies of infliximab (10 years) and etanercept (1 year) differed considerably from the mean duration of 4 years in the anakinra study. Patients in the infliximab study were more likely to receive corticosteroids than in the other 2 trials. Moreover, the infliximab study was conducted in combination with methotrexate (MTX), whereas etanercept and anakinra were evaluated as monotherapy. Forty percent of patients in the etanercept study had received previous DMARD, but none had been treated with MTX. In comparison, 66% of patients in the anakinra study had been treated previously with DMARD, mostly MTX. Finally, study duration differed: 54 weeks for infliximab, 52 weeks for etanercept, and 24 weeks for anakinra.

In the infliximab study, the effect of infliximab plus MTX was compared with MTX alone. Radiographic progression was scored in hands and feet using the van der Heijde modification of the Sharp method[14,15]. The total score, according to this modification, ranges from 0 to 440, with erosions ranging from 0 to 280 and joint space narrowing from 0 to 160. At the standard infliximab dose of 3 mg/kg every 8 weeks, combination infliximab–MTX therapy significantly slowed the change from baseline to week 54 in total Sharp score as compared with MTX alone (7.0 vs 1.3; $p < 0.001$) (Table 3)[12]. Similarly, combination therapy was significantly better than MTX alone in slowing progression of the erosion (4.0 vs 0.2; $p < 0.001$) and joint space narrowing (2.9 vs 1.1; $p < 0.001$) scores.

Etanercept monotherapy was compared with MTX alone in patients with early RA[13]. Radiographic damage was scored in hands and feet using the van der Heijde modified Sharp method with erosions being evaluated in 46 joints and joint space narrowing in 42 joint spaces. In this study, the total score ranged from 0 to 398, with erosions ranging from 0 to 230 and joint space narrowing from 0 to 168. Notably, radiographic progression in patients enrolled in this study differed considerably from those in the infliximab study. In the control MTX groups, the modified Sharp score increased

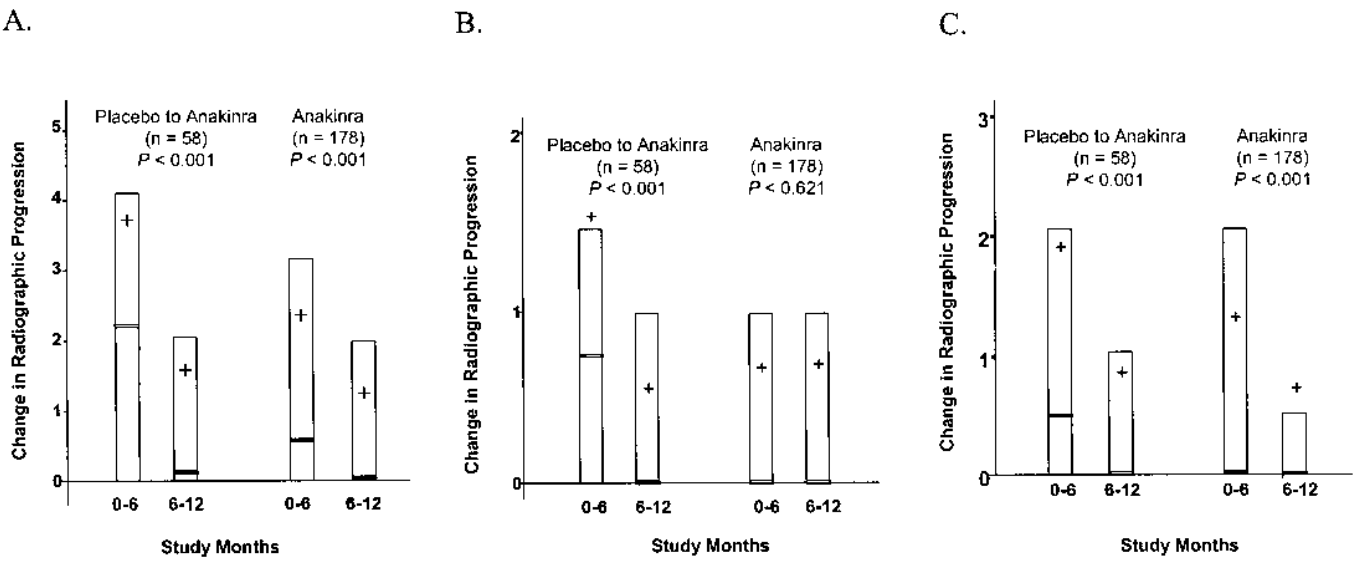

Figure 2. Change in radiographic progression during 2 consecutive 6 month intervals. Shown are the changes in Sharp total score (panel A), joint space narrowing score (B), and erosion score (C). Fifty-eight patients received placebo in the first 6 month interval and then were switched to anakinra for the second interval, whereas 178 patients continued anakinra therapy during both intervals. The mean and median changes are indicated by "+" and double line, respectively. The top and bottom of the axes represent the 75th and 25th percentiles, respectively. P values were determined using the Wilcoxon sign-rank test for equal median change from the first (months 0–6) to second (months 7–12) intervals.

Table 2. Comparison of studies of TNF-α blockers and anakinra on radiographic progression in RA.

	Infliximab (I) (Lipsky[12])	Etanercept (E) (Bathon[13])	Anakinra (A) (Bresnihan[9])
RA duration, yrs	10 (± 8)	1.0 (± 0.9)	4.1 (± 2.4)
Baseline CRP, mg/dl	3.9 (± 3.4)	3.3 (± 4.0)	4.1 (± 3.8)
Corticosteroids, %	63	39	41
Therapy	Combination (I + MTX)	Monotherapy (E vs MTX)	Monotherapy (A vs placebo)
Study duration, wks	54	52	24
Radiographic evaluation	Hands and feet	Hands and feet	Hands
Modified Sharp score, range	0–440	0–398	0–202

CRP: C-reactive protein; MTX: methotrexate.

Table 3. Prevention of joint damage by cytokine-targeted therapy.

	Infliximab (I) 54 wk, 3 mg/kg q8wk (iv)		Etanercept (E) 52 wk, 25 mg biw (sc)		Anakinra (A) 24 wk, 150 mg qd (sc)	
	MTX	I+MTX	MTX	Etanercept	Placebo	Anakinra
Sharp score range	0 to 440		0 to 398		0 to 202	
Sharp total score	7.0	1.3*	1.6	1.0	3.6	1.8*
Erosion score	4.0	0.2*	1.0	0.5†	2.0	1.1§
JSN score	2.9	1.1*	0.6	0.6	1.6	0.7*

MTX: methotrexate; JSN: joint space narrowing. * $p < 0.001$; † $p = 0.002$; § $p < 0.01$.

by 7.0 in the infliximab study but by 1.6 in the etanercept study (Table 3). During the 52 week study, etanercept significantly slowed erosions as compared with MTX (0.5 vs 1.0; $p = 0.002$), but there was no difference between treatments in joint space narrowing (0.6 in both groups). The change in total Sharp score was 1.0 with etanercept and 1.6 with MTX ($p = 0.11$).

As described above, the evaluation of anakinra relative to placebo was conducted over 24 weeks, and involved analysis of hand joints on a modified Sharp scale ranging

from 0 to 202[10]. The change from baseline in total score over 24 weeks in the placebo group was 3.6 (Table 3). If this score is annualized and the scoring range expanded to 400 to match the methods used in the infliximab and etanercept studies, then the change in total Sharp score in the placebo group would calculate to nearly 15. Accordingly, it is likely that the patients enrolled in the anakinra study were similar to or perhaps more severe than those recruited for the infliximab study. However, a placebo-alone group was not included in the infliximab study, and therefore any comparisons across studies are highly speculative.

CONCLUSION

The large differences in study design, patient selection, and outcome measures make it difficult to compare published clinical trials of cytokine-targeted therapies in RA. Nevertheless, the results of these studies indicate that IL-1 inhibition, like TNF-α inhibition, effectively suppresses the pathophysiological mechanisms associated with cartilage degradation and bone erosion, and as a consequence, radiographic progression of active RA is significantly slowed during treatment with therapies targeting either IL-1 (anakinra) or TNF-α (infliximab or etanercept).

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