Tides of Inflammation: Impact of Biologics

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ABSTRACT. Increased knowledge about the mechanisms of joint inflammation and damage has profoundly shaped the development of new therapies for rheumatoid arthritis (RA). The first stop on this remarkable bench-to-bedside journey has been the biologics targeting tumor necrosis factor-α (TNF-α) and interleukin 1 (IL-1). These engineered adaptations of naturally occurring molecules function to neutralize the biological activity of proinflammatory cytokines overproduced in the joints of patients with RA. The successful translation of this approach into the clinic has had a substantial effect on the care of patients with RA. (J Rheumatol 2002;29 Suppl 65:22-26)

Key Indexing Terms:
ANAKINRA ETANERCEPT INFLIXIMAB
CYTOKINES RHEUMATOID ARTHRITIS

The first tumor necrosis factor-α (TNF-α) and interleukin 1 (IL-1) inhibitors to reach the clinic are etanercept, infliximab, and anakinra. Etanercept, a TNF-α antagonist, consists of a dimer of the extracellular domain of the soluble TNF receptor II fused to a human IgG1 Fc region. The soluble receptor binds extracellular TNF-α and neutralizes its effects. Infliximab, a chimeric anti-TNF-α antibody, is formed from a mouse antigen-binding region (Fv) covalently linked to a human IgG1 Fc region. This antibody binds to soluble as well as membrane-bound TNF-α. Anakinra, a recombinant human IL-1 receptor antagonist (IL-1ra), occupies the IL-1 receptor without activating it and keeps IL-1 from binding to the receptor and eliciting a biological response.

Etanercept, infliximab, and anakinra have each been approved for the treatment of rheumatoid arthritis (RA). Among the different classes of antirheumatic drugs, they may be considered as disease modifying antirheumatic drugs (DMARD) because of their capacity to slow the radiological progression of joint damage. These potent antiinflammatory agents are quite versatile in their potential for other clinical applications. Etanercept, the first biologic to be approved for the treatment of RA, has also been shown effective for the treatment of juvenile rheumatoid arthritis and more recently, for the treatment of psoriatic arthritis. Two years before its approval for treating RA, infliximab was approved for the treatment of Crohn's disease. Anakinra, the latest to join the ranks of approved biologics for RA therapy, has not been approved for other clinical indications. This review, however, will focus on the efficacy of these biologics for the treatment of RA.

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Supported by an unrestricted educational grant from Amgen, Inc.

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IMPROVEMENT IN SIGNS AND SYMPTOMS

The evidence that TNF-α and IL-1 antagonists can ameliorate the signs and symptoms of RA confirms the traditional view of RA pathogenesis that excessive amounts of proinflammatory cytokines overwhelm the system of naturally occurring cytokine inhibitors. Etanercept itself is derived from a natural cytokine inhibitor, the soluble TNF-α receptor II. Etanercept has been investigated as a single DMARD therapy for RA and in combination with methotrexate (MTX). Initial studies enrolled mostly patients with a median disease duration of 8–10 years, or established disease. An important lesson from these initial trials was that within 1–2 months of withdrawal of etanercept, a disease relapse occurs, indicating that continuous TNF-α blockade is required to sustain clinical improvement.

In a pivotal trial, twice-weekly subcutaneous injections of etanercept 10 mg or 25 mg were compared with placebo in a 6 month, randomized, placebo controlled study involving 234 patients with active RA[1]. In this study, the etanercept 25 mg group achieved an American College of Rheumatology (ACR) 20 response rate of 59% at the 6 month endpoint compared with an 11% rate for the placebo group ($p < 0.001$). The etanercept 10 mg group had a lower rate of response than the etanercept 25 mg group. Etanercept has also been shown effective for the treatment of patients with active RA receiving concomitant treatment with MTX. In a 6 month, randomized, placebo controlled trial, adding etanercept 25 mg to stable doses of MTX therapy produced a significantly higher ACR20 response rate than the comparison MTX plus placebo group (71% vs 27%; $p < 0.001$)[2]. These data attest to the potent antiinflammatory effects of etanercept therapy.

Attention shifted to the potential value of etanercept therapy for patients with relatively early disease. This interest arose from the appreciation that joint destruction and disability occur early in the course of RA. In choosing an initial DMARD therapy, most rheumatologists would view MTX as the standard of care for treatment of patients

with disease of at least moderate activity. The question of the most effective therapy for early disease was posed in a 12 month, randomized, double blind trial comparing etanercept and MTX therapy for patients with active RA of less than 3 years' duration (Early RA Trial, ERA)[3]. No significant differences were found in the ACR20 response rates between the etanercept 25 mg and MTX groups at the 12 month endpoint (72% vs 65%; p = NS). ACR50 and ACR70 response rates were also no different between the treatment groups. These results indicate that etanercept and MTX therapy are similarly effective in relieving the signs and symptoms of early disease.

Infliximab therapy for RA has been most often investigated in combination with MTX. A preference for this approach came from concerns that treatment with infliximab alone would frequently induce anti-infliximab antibodies and that concomitant MTX therapy would suppress this undesirable response[4]. However, this hypothesis has not been formally tested in a clinical trial. The Anti-TNF Trial in RA with Concomitant Therapy (ATTRACT), the largest completed study of infliximab to date, enrolled 428 patients with active RA whose disease was only partially controlled with MTX therapy[5,6]. In this randomized, double blind trial, patients were randomly allocated to 5 different treatment groups: placebo or infliximab 3 mg/kg or 10 mg/kg every 4 or 8 weeks. The study drug infusions were administered at week 0, 2, and 6 and then every 4 or 8 weeks. MTX therapy was maintained at the entry dose (mean of 16–17 mg/week) for the duration of the trial. At week 54, the ACR20 response rates for the infliximab treatment groups ranged from 42% to 59%, significantly higher than the 17% rate for the placebo group[5] (Figure 1A). There were no statistically significant differences in ACR20 response rates among the 4 infliximab treatment groups; however, the ACR50 response rate was significantly lower in the 3 mg/kg every 8 week group (21%) than the 3 higher infliximab dosage groups (34%, 39%, and 38% for 3 mg/kg every 4 weeks, 10 mg/kg every 8 weeks, and 10 mg/kg every 4 weeks, respectively) (Figure 1A). Overall, infliximab therapy produced clinical improvement that occurred rapidly and was sustained throughout the 54 week trial period.

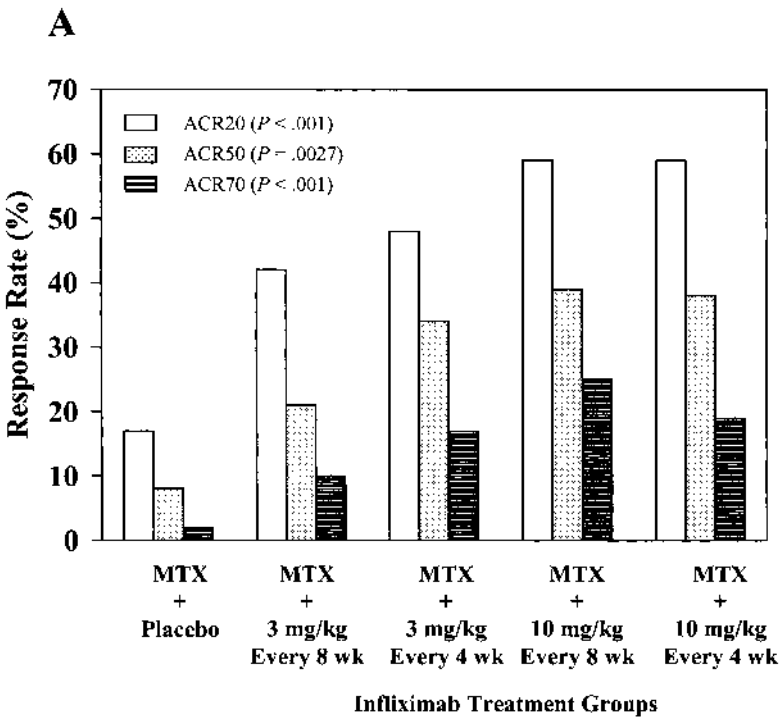
Anakinra has been evaluated in 3 randomized, double blind, placebo controlled studies. The clinical efficacy of anakinra was first shown in a 24 week dose-ranging study involving 472 patients with active RA[7]. After a 6 week DMARD washout, patients were randomly allocated to receive daily subcutaneous injections of placebo or 30 mg, 75 mg, or 150 mg of anakinra. ACR20 response rates ranged from 34% to 43% among the anakinra treatment arms compared with a 27% rate for the placebo group. Only the ACR20 response rate for the 150 mg anakinra treatment group was significantly higher than that of the placebo group (43% vs 27%; p = 0.014). The ACR50 response rate was also higher for the 150 mg anakinra treatment group than the placebo group (19% vs 8%; p < 0.05).

Anakinra has also been evaluated in combination with MTX. In an early 24 week dose-ranging study, 419 patients with active RA and taking stable doses of MTX were randomly allocated to receive daily subcutaneous injections of placebo or 0.04, 0.1, 0.4, 1.0, or 2.0 mg/kg anakinra[8]. Compared with the placebo group, ACR20 response rates were significantly higher for the anakinra 1.0 and 2.0 mg/kg groups (Figure 1B). These results prompted a 506 patient, double blind, placebo controlled trial of the 1.0 mg/kg dose in combination with MTX therapy[9]. At week 24, the ACR20 response rates were significantly higher in the anakinra treatment group compared with the placebo group (38% vs 22%; p < 0.001). On the basis of these results, anakinra has been approved for the treatment of RA both alone and in combination with MTX therapy.

EFFECTS ON JOINT DAMAGE

A crucial finding from these studies is that these new biologics can slow the radiological progression of joint damage. The inference from keeping joint damage in check is that it ultimately correlates with superior physical function and quality of life. However, the relationship between the change in damage scores and functional status is imprecise (especially in early disease) and will require further study to improve our understanding of the radiological outcomes. In these trials, joint damage is typically scored from plain radiographs of the hands (and often the feet), using either the modified Sharp[10] or Larsen score[11]. Both scales are validated measures of joint damage. The Larsen score uses a 6 point scale of increasing joint damage, based mainly on the extent of bone destruction. On the other hand, the modified Sharp score includes a separate component for erosive damage (6 point scale) and joint space narrowing (5 point scale), which are combined to yield a total Sharp score. The outcomes are reported on a group level (mean or median change in score), with efficacy based on finding a statistically significant difference in the change in scores between treatment groups.

An important question in the ERA trial[3] focused on the relative efficacy of etanercept and MTX therapy for preventing joint destruction. MTX therapy had been shown to reduce the radiological progression of joint damage in previous trials involving patients with established RA[12]. The treatment groups in the ERA trial represented a population of patients with early disease. They had a mean duration of disease of 12 months and a predicted annual rate of progression of 9, 5, and 4 for the total Sharp score, erosion score, and narrowing score, respectively. This predicted rate comes from dividing the Sharp score at baseline by the disease duration. However, with a short duration of disease, these estimates can be prone to error. A small discrepancy at this stage between the suspected and actual duration of disease



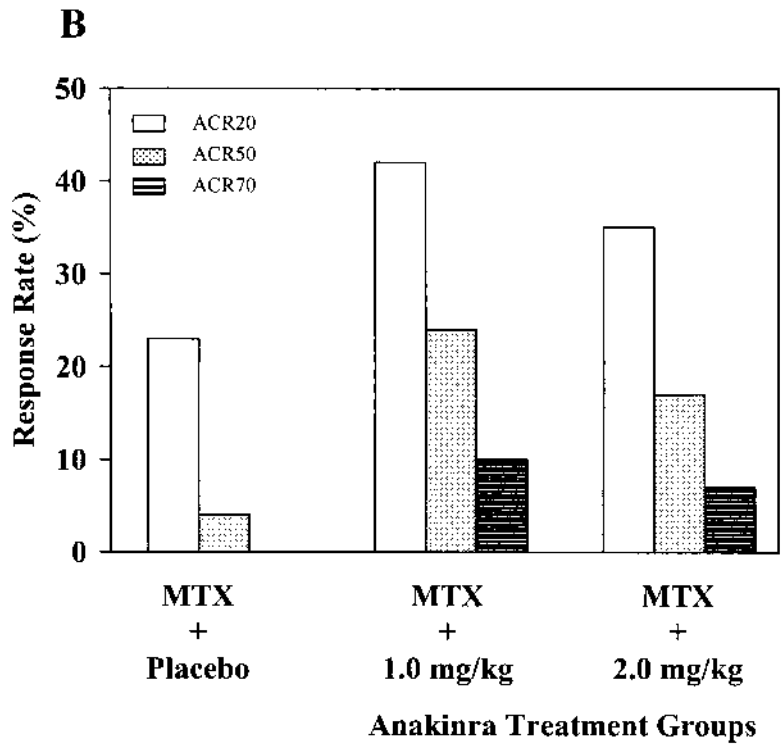


Figure 1. Clinical improvement with TNF-α and IL-1 targeted therapies for RA. A. Results from ATTRACT[6] comparing ACR20, ACR50, and ACR70 response rates at week 54 for the 4 infliximab treatment groups versus placebo. All patients continued to receive concomitant MTX therapy. The response rates were significantly higher for each of the infliximab treatment groups than for the placebo group. B. Results from a dose-ranging trial of anakinra in combination with MTX therapy[7]. Only the response rates are shown for the placebo and the 1.0 mg/kg and 2.0 mg/kg anakinra treatment groups, the 2 highest dosages of anakinra used in the trial. The ACR20 response rates were significantly higher for the anakinra 1.0 mg/kg and 2.0 mg/kg groups compared to placebo ($p = 0.039$ and $p = 0.013$, respectively).

can produce relatively large errors in this estimate. For the ERA trial, radiographs of the hands and feet were obtained at baseline, 6 months, and 12 months. The primary endpoint for this analysis was the change at 12 months in total Sharp score. A linear extrapolation, based on the rate of change in Sharp score between the first and last observations, was used for patients who withdrew from the study. Only 15 (2%) of the 632 patients in this study had no followup radiographs.

The results showed no significant differences in the change in total Sharp score between the etanercept 25 mg and MTX treatment groups[3]. In a secondary analysis, the mean increase in erosion score at 12 months was found to be significantly less in the etanercept 25 mg than the MTX group (0.47 vs 1.03; p = 0.002). In the MTX group, the rate of change in the erosion score was also shown to be significantly less during the second 6 months than the first 6 months of the study. The rate of change in the erosion score for the MTX group for the second 6 months was similar to that of the etanercept 25 mg group during the same period. In contrast, the changes in the joint space narrowing scores were not significantly different between the etanercept 25 mg and MTX treatment groups (1.00 vs 1.59; p = 0.11). The patients receiving etanercept 25 mg and MTX showed less of an increase in Sharp scores over 12 months than was predicted at baseline, suggesting both treatments were effective in reducing joint damage.

When added to MTX therapy, infliximab has been shown to slow the rate of joint destruction. In ATTRACT, the effects of infliximab therapy on joint damage were assessed in the hands and feet, using a modified Sharp score[9]. Of the 428 patients, 349 (82%) contributed radiographs to this analysis. At week 54, the mean change in total Sharp score was significantly less for each of the infliximab treatment groups compared with the placebo group[6] (Table 1). Infliximab favorably influenced both the erosion and joint space narrowing scores (Table 1). In a subgroup analysis, infliximab was found to delay the progression of joint damage in patients without an ACR20 response, implying an uncoupling of the mechanisms controlling inflammation and destruction. This result, however, must be viewed with caution, because it represents a post-hoc analysis. Also, a proportion of the ACR20 nonresponders may have had clinical improvement in inflammatory manifestations despite failing to meet the response criteria. Regardless, this study confirms that TNF-α plays a key role in the pathogenesis of bone and cartilage destruction in the joint.

Treatment with anakinra also appears to have a beneficial effect on the rate of joint destruction. In the study described above, the rate of progression of joint damage was compared among patients receiving daily subcutaneous injections of placebo or 30 mg, 75 mg, or 150 mg anakinra[7]. To be eligible, the 472 patients in this trial must have withdrawn DMARD therapy at least 6 weeks before entry. Radiographs of the hands and wrists were taken at baseline and at week 24 and scored by 2 trained readers using the Larsen method[10]. A complete set of radiographs was available from 347 (74%) of the 472 patients in the placebo and 30 mg, 75 mg, and 150 mg anakinra treatment groups. No significant differences were found in the change in Larsen score between the placebo group and the 30 mg, 75 mg, or 150 mg anakinra treatment groups. However, in an exploratory analysis, the combined 3 groups of patients treated with anakinra were shown to have a significantly lower rate of radiological progression of joint damage than the placebo group[7]. The increase in mean Larsen score was 3.8 for the combined anakinra group and 6.4 for the placebo group, which corresponded to a 41% reduction in the rate of radiological progression of joint damage for the patients treated with anakinra. An additional post-hoc analysis using a modified Sharp score showed similar trends in radiological outcomes. These results suggest anakinra, like the TNF-α inhibitors, delays the progression of joint damage.

Additional studies are needed to confirm these positive findings over longer periods of time. Also, a clinical trial is in progress to evaluate the joint protective effects of anakinra in combination with MTX therapy.

Table 1. Radiological Responses at 54 Weeks in ATTRACT [6]

		Infliximab Dose			
	Placebo Plus MTX	3 mg/kg, q8w Plus MTX	3 mg/kg, q4w Plus MTX	10 mg/kg, q8w Plus MTX	10 mg/kg, q4w Plus MTX
Total Sharp score					
Mean change	7.0 ± 10.3	1.3 ± 6.0*	1.6 ± 8.5*	0.2 ± 3.6*	–0.7 ± 3.8*
Median change	4.0	0.50*	0.09*	0.50*	–0.50*
Erosion score					
Mean change	4.0 ± 7.9	0.2 ± 2.9*	0.3 ± 4.7*	0.2 ± 2.9*	–0.7 ± 3.0*
Median change	2.0	0.0*	0.0*	0.50*	–0.50*
Joint space narrowing					
Mean change	2.9 ± 4.2	1.1 ± 4.4	0.7 ± 4.3	0.0 ± 3.1	0.0 ± 2.5
Median change	1.5	0.0†	0.0*	0.0*	0.0*

p value vs MTX alone: * p < 0.001; † p = 0.001. MTX: methotrexate.

CONCLUSION

The results from clinical trials show that targeting TNF-α and IL-1 can relieve the signs and symptoms of RA, as well as delay the progression of joint damage. While tempting, it is difficult to compare the efficacy of the TNF-α targeted therapies with anakinra because of differences across studies in patient populations, study designs, and outcome measures. Rather than focusing on their relative efficacy, the challenge now is to develop a means to individualize therapy for optimal clinical response. Can patient-specific tests, such as the identification of genetic polymorphisms, be developed to predict the response to TNF-α and IL-1 inhibitor therapy? What are the advantages and disadvantages of combining a TNF-α and an IL-1 antagonist? Do these cytokine antagonists prevent joint destruction independent of their antiinflammatory effects? Working toward the answers to these questions will likely improve longterm outcomes and lead to innovative treatment strategies.

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