Examining the Efficacy of Biologic Therapy: Are There Real Differences?

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ABSTRACT. Biologic therapy with anakinra, etanercept, and infliximab effectively reduced the signs and symptoms of active rheumatoid arthritis (RA) in randomized controlled trials. Clinical efficacy was determined by American College of Rheumatology (ACR) response criteria. In patients failing previous disease modifying antirheumatic drug (DMARD) therapy, both anakinra and etanercept were significantly more effective than placebo. In patients with inadequate responses to methotrexate (MTX), addition of anakinra, etanercept, or infliximab to stable MTX therapy was significantly more effective than MTX alone. Etanercept has also shown efficacy in early stage, methotrexate-naive patients. Comparisons of the efficacy of these biologics across clinical studies are problematic due to differences in study design, study conduct, and patient populations. Moreover, ACR response rates do not allow comparisons of agents that each achieve these responses relative to placebo. Until comparative clinical studies are conducted, in which 2 biologics are evaluated using the same protocol and patient population, the only conclusion that can be reached from published studies is whether an individual biologic agent is safe and effective. All 3 biologics — anakinra, etanercept, and infliximab — are effective. (J Rheumatol 2002;29:Suppl 65:27–32)

Key Indexing Terms:
ANAKINRA BIOLOGIC THERAPY ETANERCEPT
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The safety and efficacy of biologic therapy directed against tumor necrosis factor-α (TNF-α) or interleukin 1 (IL-1) have been established in multiple randomized controlled trials of patients with active rheumatoid arthritis (RA). TNF-α blockers infliximab, a chimeric murine anti-TNF-α monoclonal antibody, and etanercept, a recombinant soluble TNF receptor-IgG_1 Fc fusion protein, reduced the signs and symptoms of RA and slowed radiographic disease progression[1-5]. Similarly, anakinra, a recombinant human IL-1 receptor antagonist, was effective in studies using these clinical and radiographic endpoints in patients with active disease[6-8]. Cytokine inhibitors have been compared in animal models of RA, showing differences in several indices of inflammation and joint damage[9-11], but side-by-side comparisons in patients with RA have not been reported. Until such studies are conducted, there is no accurate way to compare efficacies among biologic agents. However, it is possible to determine the efficacy of each agent compared with placebo.

PITFALLS IN COMPARING STUDIES

Differences in study design, study conduct, and patient characteristics make comparisons across clinical studies problematic (Table 1). Study designs may differ in terms of the length of the study, the comparator agent, and how the study is analyzed statistically. Study conduct may differ, because some studies evaluate monotherapy with biologics, and others evaluate biologics in combination with methotrexate (MTX). Patient populations may differ in terms of disease duration and disease activity, and whether patients had been exposed to or had failed previous disease modifying antirheumatic drugs (DMARD).

The greatest difficulty in comparing clinical trials is that different studies have analyzed endpoints using different methods of statistical analysis. An intent-to-treat (ITT) analysis, in which every patient receiving at least one dose of study medication is included, is always used in a safety evaluation, but it is not necessarily used in the efficacy evaluation. Statistical methods are used in the efficacy evaluation to account for patients who discontinue drug use early due to adverse events, lack of efficacy, or other reasons. These methods include a last observation carried forward

Table 1. Pitfalls in comparing clinical trials.

Study design	Length of study
	Monotherapy
	Combination (placebo or active)
Study conduct	Statistical analysis of study
	Primary endpoint
Patient population	Disease duration
	Disease activity
	Previous DMARD
	MTX-naive

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(LOCF) analysis or a nonresponder imputation (NRI) analysis. According to the LOCF method, the last value obtained in the study is used even if the patient withdraws early from the study. In comparison, patients must complete the study and fulfill all efficacy criteria in order to be included positively in the NRI analysis. Thus, the LOCF method suggests the highest level of success that can be obtained with a therapeutic intervention (ceiling effect), whereas the NRI method suggests the lowest level of success (floor effect). Consequently, in order to compare clinical trials, the same efficacy analysis is mandatory.

There are also numerous other factors that must be considered when attempting to compare clinical trials. First, patients should have similar disease duration and activity at baseline. It would be problematic to compare patients with early-stage disease in one study with those having disease for 10 years or longer in another study. Second, patients should have similar prior drug use and concurrent therapies. Studies of patients failing multiple DMARD should not be compared with those of DMARD-naive patients. Third, in studies of combination therapy with MTX, the dose and duration of MTX should be similar in both studies. Fourth, in active controlled clinical trials, the comparator should be the same drug used at the same dose and schedule. Finally, studies having the same duration should be compared. The minimum study duration, however, will vary according to the variable under evaluation. Clinical responses should be evaluated in studies having a minimum duration of 3 to 6 months; radiographic responses should be evaluated after a minimum of 6 to 12 months; and functional responses should be assessed after at least 24 months.

CLINICAL STUDIES OF BIOLOGICS

Six studies will be considered: anakinra and etanercept in placebo controlled studies of patients failing previous DMARD[1,6]; anakinra, etanercept, and infliximab added to MTX in patients with incomplete responses to MTX alone[2,4,7]; and etanercept compared with MTX in MTX-naive patients[3]. The features of each study are shown in Table 2. Each study used an ITT analysis, but the endpoint was evaluated using an LOCF method in 2 studies and an NRI method in the other 4 trials. The studies differed in terms of disease duration, with 3 trials having no duration limit, but the anakinra studies setting a maximum duration of 8 years in the monotherapy trial and 12 years in the combination trial. The comparison of etanercept and MTX was done in patients with early stage disease, which was defined by disease duration of no more than 3 years. This was also the only study that required patients to be MTX-naive. In 3 studies, the biologic was given in combination with MTX, whereas it was used as monotherapy in the other trials. Other variables also differed considerably across studies: the study length varied from 24 to 54 weeks; the number of patients per study ranged from 89 to 632; and the number of previous DMARD varied from 0.5 to 3. The mean tender and swollen joint counts were lower in the studies of patients taking background MTX therapy than in the studies of monotherapy. In each study, stable doses of nonsteroidal antiinflammatory drugs and prednisone (≤ 10 mg daily) were allowed.

The American College of Rheumatology (ACR) 20% response is used to evaluate whether a medication is effective on the clinical signs and symptoms of RA[12]. An ACR20 response is defined by at least 20% decreases in the swollen and tender joint count, and at least 20% improvements in 3 of the following 5 criteria: physical disability on the Health Assessment Questionnaire; pain score on a visual analog scale; patient global assessment; physician global assessment; and acute phase reactant [either erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)]. It should be recognized that the ACR20 was designed to separate the activity of a DMARD from placebo in a randomized double blind trial in a group of patients with RA. It does not allow comparisons between drugs that each achieves ACR20 responses relative to placebo. Clearly, the ACR20 does not have relevance to an individual being treated in the clinic. Almost all patients who reach an ACR20 response have more than a 20% improvement in the individual components

Table 2. Comparisons of study design, study conduct, and patient populations in 6 studies of biologic therapy.

	Anakinra Monotherapy	Etanercept Monotherapy	Anakinra Plus MTX	Etanercept Plus MTX	Infliximab Plus MTX	Etanercept Versus MTX
ITT analysis	Yes	Yes	Yes	Yes	Yes	Yes
Endpoint analysis	LOCF	NRI	NRI	NRI	NRI	LOCF
Disease duration, yrs	8	No limit	12	No limit	No limit	3
Comparator	Placebo	Placebo	MTX	MTX	MTX	MTX
MTX-naive	No	No	No	No	No	Yes
Length of study, wks	24	26	24	26	54	52
Patients, No. enrolled	472	234	419	89	428	632
Previous DMARD	NA	3.0–3.4	1.4–2.1	2.7–2.8	3.0	0.5
Mean tender joint count	33–39	33–35	22–28	28	32	30–31
Mean swollen joint count	26	25	17–19	17–20	20	24

LOCF: last observation carried forward; NRI: nonresponder imputation.

of the ACR criteria. For instance, patients can have an 80% improvement in tender joint count, 80% improvement in swollen joint count, 80% improvement in ESR, 80% improvement in patient assessment of pain, and 49% improvement in all other characteristics, and, for the purpose of study outcome, they will be considered ACR20.

STUDIES OF BIOLOGICS IN PATIENTS FAILING DMARD

Anakinra and etanercept have each been evaluated in randomized placebo controlled trials of patients failing previous DMARD therapy[1,6]. The anakinra study enrolled 472 patients with RA based on the ACR criteria[6]. Eligible patients had disease duration of 0.5 to 8 years, and had failed up to 3 previous DMARD. Patients had active disease as defined by 10 or more swollen joints and at least 3 of the following criteria: 10 or more tender/painful joints; disease activity graded as severe or very severe by the patient or physician; and CRP > 1.5 mg/dl. Patients were randomly assigned to receive anakinra 30, 75, or 150 mg, or placebo, given by daily subcutaneous injection for 24 weeks. The primary endpoint was the ACR20 response at 24 weeks.

Patients treated with anakinra 150 mg had a significantly higher ACR20 response rate as compared with placebo (43% vs 27%; p = 0.014)[6]. The ACR20 response rates with anakinra 30 mg (39%; p = 0.054) and 75 mg (34%; p = 0.258) did not achieve statistical significance relative to placebo. However, when the 3 anakinra groups were combined, the ACR20 response rate was significantly higher than placebo (p = 0.020). Notably, patients in each of the anakinra groups responded quickly to treatment. ACR20 responses were evident within 2 to 4 weeks of treatment; the rate tended to plateau after 12 to 16 weeks. Thus, this study demonstrated that anakinra monotherapy showed significant efficacy on the basis of the ACR20 response at the 24 week endpoint.

Etanercept monotherapy was evaluated in a study of 234 patients with active RA[1]. Patients meeting ACR criteria of RA were eligible if they had at least 10 swollen joints, at least 12 tender joints, and at least one of the following: ESR ≥ 28 mm/h, CRP > 2.0 mg/dl, or morning stiffness of at least 45 min. Patients were required to have failed one to 4 previous DMARD, but there was no limit on disease duration (mean 12 yrs). Patients were randomly assigned to receive etanercept 10 or 25 mg or placebo given by twice weekly subcutaneous injection for 6 months. The primary endpoints were the ACR20 and ACR50 response rates at 3 and 6 months. Etanercept 10 and 25 mg produced significantly higher ACR20 response rates than placebo at 6 months (51% and 59% vs 11%; p < 0.001). In addition, both doses were significantly better than placebo in terms of ACR50 response rates (24% and 40% vs 5%; p < 0.001). Significant ACR20 responses were evident after 2 weeks of etanercept therapy. On the basis of these ACR20 and ACR50 responses, it can be concluded that etanercept monotherapy has significant efficacy.

STUDIES OF BIOLOGICS IN COMBINATION WITH METHOTREXATE

Combination therapy with anakinra, etanercept, or infliximab was evaluated in patients who were controlled incompletely by MTX[2,4,7]. The biologic or placebo was added to existing stable doses of MTX, and activity was assessed by comparing the biologic–MTX combination with MTX alone (placebo group). The study of anakinra enrolled 419 patients with RA who had been receiving MTX 15 to 25 mg weekly for at least 3 months[7]. Eligible patients had RA for 0.5 to 12 years, and despite MTX, they had 6 or more swollen joints, and at least 2 of the following: 9 or more tender/painful joints, CRP > 1.5 mg/dl, or morning stiffness of at least 45 min. Patients were randomly assigned to receive anakinra 0.04, 0.1, 0.4, 1.0, or 2.0 mg/kg or placebo daily in addition to their weekly MTX dose. The study was originally designed to last for 12 weeks, but it was extended to 24 weeks. The primary efficacy endpoint was the ACR20 response at 12 weeks, with the ACR20 at 24 weeks being a secondary endpoint.

Adding anakinra to MTX produced a significant dose dependent increase in the ACR20 response rate at week 12 relative to adding placebo (p = 0.0013)[7]. At the 2 highest doses, anakinra provided significantly higher ACR20 responses than placebo (46% at 1 mg/kg and 38% at 2 mg/kg vs 19% with placebo; p = 0.001 and 0.007, respectively). At 24 weeks, these doses remained significantly more effective than placebo regardless of whether ACR20, ACR50, or ACR70 responses were measured (Figure 1).

Combination etanercept–MTX therapy was evaluated in a relatively small study of 89 patients who remained symptomatic despite stable MTX doses of 15 to 25 mg weekly for at least 6 months[2]. A MTX dose of 10 mg weekly was allowed for patients unable to tolerate a higher dose. Eligible patients had at least 6 swollen and 6 tender joints, in spite of MTX therapy. Patients were randomly assigned in a 2:1 ratio to receive etanercept 25 mg or placebo twice weekly for 24 weeks in addition to continuing their stable MTX dose. The primary endpoint of the study was safety of the combination of etanercept and MTX versus MTX alone. The secondary endpoint was the ACR20 response at 24 weeks. Combination therapy produced significantly higher ACR20 responses than MTX alone (71% vs 27%; p < 0.001). Combination therapy also gave higher ACR50 (39% vs 3%; p < 0.001) and ACR70 (15% vs 0%; p = 0.03) responses.

Infliximab was added to MTX in a randomized MTX controlled (rather than placebo controlled) study of 428 patients with active RA despite receiving MTX for 3 or more months, with stable doses of 12.5 mg weekly or higher for at least 4 weeks[4]. Eligible patients had disease for at least

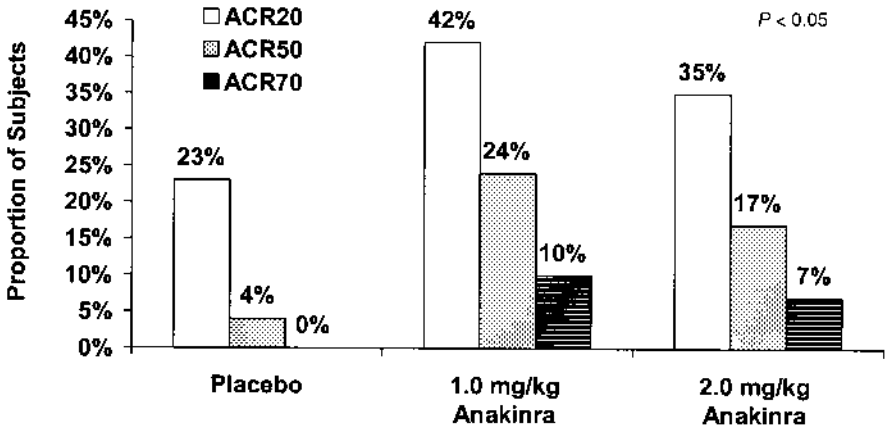

Figure 1. ACR responses with combination anakinra–MTX therapy as compared to MTX alone (placebo). From Cohen, *et al*[7], with permission.

6 months and had failed more than one previous DMARD. Patients had at least 6 tender and 6 swollen joints and 2 of the following: ESR ≥ 28 mm/h, CRP > 2 mg/dl, or morning stiffness of at least 45 min. Patients were randomly assigned to receive infliximab 3 or 10 mg/kg or placebo every 4 or 8 weeks in addition to continuing their stable dose of MTX. Primary endpoints in this study included the ACR20 at 30 weeks, radiographic analysis at 54 weeks, and functional analysis using the HAQ at 102 weeks. After 30 weeks, the ACR20 response was significantly higher with combination therapy, independent of the dose or schedule of infliximab, as compared to MTX alone (50%–58% vs 20%; $p < 0.001$). By 54 weeks, however, it appeared that the ACR responses in the 3 mg/kg groups were somewhat lower than in the 10 mg/kg groups, even though they were still significantly higher than with MTX alone (Table 3). It is important to recognize, however, that an NRI analysis was used, and therefore patients discontinuing before 54 weeks were counted as having zero response.

All studies indicated that combination therapy, regardless of whether anakinra, etanercept, or infliximab is added to MTX, is effective in reducing the signs and symptoms of RA as compared to MTX alone. The activity was evident in the ACR20 response rates, as well as when the more stringent ACR50 and ACR70 criteria were used.

ETANERCEPT VERSUS MTX IN EARLY RA

Etanercept was compared with MTX in a randomized controlled study of 632 patients with RA duration up to 3 years[3]. Eligible patients had 10 or more swollen joints, 12 or more tender joints, positive rheumatoid factor or at least 3 bone erosions on baseline radiographs, and one of the following: ESR ≥ 28 mm/h, CRP ≥ 2 mg/dl, or morning stiffness of at least 45 min. Patients were randomly assigned to receive etanercept 10 or 25 mg twice weekly or MTX, which was titrated from 7.5 mg to 20 mg weekly over an 8 week period. A double dummy design was used to ensure blinding. The primary clinical endpoint was the integrated area of the ACR response over 6 months. Etanercept produced a more rapid onset of action than MTX, with significant differences in ACR response rates between treatments being evident by 2 weeks and lasting for 4 months ($p < 0.05$) (Figure 2). Both etanercept and MTX achieved significantly higher ACR 20 responses than any of the previous trials discussed. This may well be a direct result of early and aggressive treatment — again a different study design. After 4 months, ACR20, ACR50, and ACR70 response rates did not differ significantly between etanercept and MTX in the first year of the study but maintained their high rate of response through the entire 12 months. The high rate of response may also be explained, in part, by the fact that the LOCF method was used for statistical analysis.

PROBLEMS WITH COMPARISONS ACROSS STUDIES

The studies of anakinra and etanercept in patients failing previous DMARD cannot be compared for several reasons[1,6]: different statistical efficacy evaluations; different disease durations from study to study; different quantitative information regarding prior DMARD failures; different

Table 3. ACR responses with combination infliximab-MTX therapy versus MTX alone at 54 weeks (From Lipsky, *et al*[5], with permission. Values are the percentage of patients.

	ACR20	ACR50	ACR70
MTX	17	8	2
+Infliximab 3 mg/kg q8 weeks	42**	21*	10*
+Infliximab 3 mg/kg q4 weeks	48**	34**	17**
+Infliximab 10 mg/kg q8 weeks	59**	39**	25**
+Infliximab 10 mg/kg q4 weeks	59**	38**	19**

* $p < 0.05$;
** $p < 0.001$.

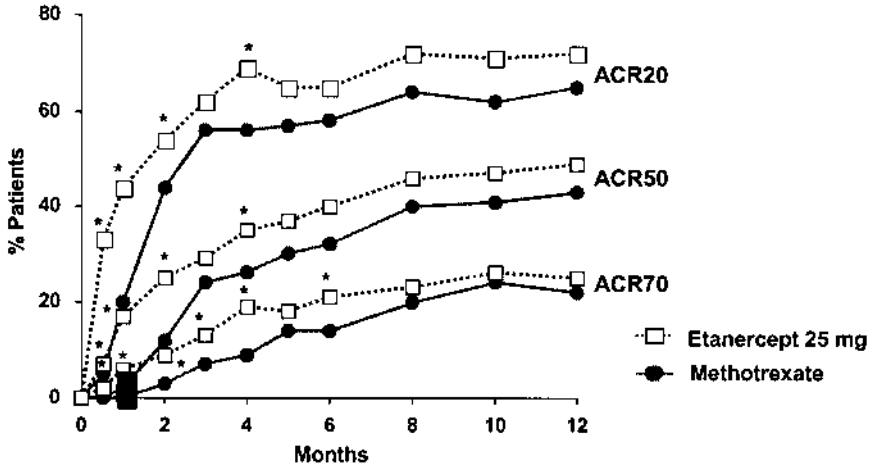

Figure 2. ACR responses with etanercept versus MTX in patients with early RA. *p < 0.05. From Bathon, *et al*[3], with permission.

criteria of disease activity to qualify patients for these studies; and the etanercept study had a higher placebo withdrawal rate than the anakinra study (68% vs 32%).

Similarly, the studies of combination therapy in patients with inadequate responses to MTX cannot be compared[2,4,7]. First, each study involved patients with a different mean duration of disease (7 yrs in the anakinra study, 13 yrs in the etanercept study, and 8 yrs in the infliximab study). Second, each used a different mean dose of MTX (17 mg in the anakinra study, 18–19 mg in the etanercept study, and 15 mg in the infliximab study). Third, patients in these studies failed a different number of previous DMARD. Fourth, the inclusion criteria of disease activity differed among the studies. Finally, the studies of anakinra and infliximab were designed to evaluate efficacy, whereas the trial of etanercept was designed as a safety study.

The comparative study of etanercept versus MTX was the only study that involved MTX-naive patients and the only study that limited disease duration to 3 years[3]. The comparator was the early use of an aggressive dosed MTX regimen. Thus, the study design, study conduct, and patient population differed from those of the other trials, and consequently, it cannot be compared directly with any of the others.

The substantial differences in study design and patient population among the studies makes any interpretation of comparative activity highly speculative. If, however, one compares studies by examining the confidence interval of 2 standard deviations from the mean ACR response in each study (Figure 3), one can speculate that their efficacy is fairly similar.

CONCLUSION

The published studies of anakinra, etanercept, and infliximab cannot be compared accurately, because they differ

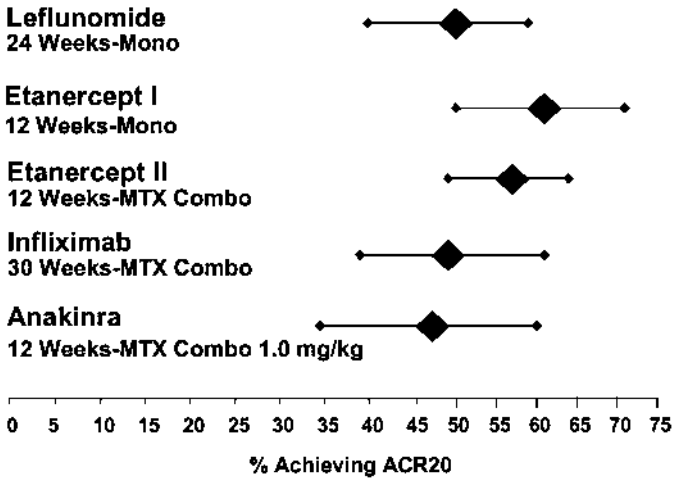

Figure 3. Percentage of study patients achieving ACR20 scores. Comparison of studies suggests that ACR20 scores for biologics are largely comparable. Based on exact 95% confidence intervals, SAS version 8.0.

substantially in study design, study conduct, and baseline patient characteristics. On the basis of ACR responses, it can be concluded that: anakinra is effective as monotherapy and when administered in combination with MTX; etanercept is effective as monotherapy, in combination with MTX, and in early RA; and infliximab is effective in combination with MTX. In order to accurately compare 2 biologics, a study must be undertaken which includes both agents in the same protocol having a consistent design, conduct, and patient population. At present, the only conclusion that can be reached from published studies is whether an individual biologic is effective and safe. All 3 agents appear to be effective.

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