Clinical Outcomes of Patients with Rheumatoid Arthritis After Switching from Infliximab to Etanercept

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ABSTRACT. ***Objective.*** To assess the efficacy and monitor serious adverse events in patients with rheumatoid arthritis (RA) switching treatment from infliximab to etanercept.

Methods. Adult patients with active RA who were discontinuing treatment with infliximab were eligible to enroll in this prospective, 12-week, open label, single-arm, observational study. Four to 10 weeks after their last infusion of infliximab, patients began treatment with etanercept (twice weekly subcutaneous injections of 25 mg). Clinical assessments using the American College of Rheumatology (ACR) criteria for improvement were performed at baseline and at Weeks 6 and 12, and serious adverse events were monitored throughout the study.

Results. Twenty-five patients were enrolled, 18 of whom had discontinued infliximab because of lack of efficacy, and 22 completed 12 weeks of etanercept treatment. After 12 weeks, 14 of 22 patients (64%) achieved at least a 20% improvement in ACR criteria (ACR20), 13 (59%) experienced improvements in physical function that were considered clinically important (≥ 0.22 point decrease in overall Health Assessment Questionnaire score), and mean values of all individual components of the ACR criteria had improved. No serious adverse events were reported during the study and no patient discontinued because of lack of efficacy.

Conclusion. Etanercept, a soluble tumor necrosis factor (TNF) receptor, provided a well tolerated and effective treatment option for some patients even when infliximab, a monoclonal antibody to TNF, had been ineffective. (J Rheumatol 2004;31:2356–9)

Key Indexing Terms:
TUMOR NECROSIS FACTOR — RHEUMATOID ARTHRITIS
ANTIRHEUMATIC AGENTS — ETANERCEPT — INFLIXIMAB

Tumor necrosis factor (TNF) is a proinflammatory cytokine that plays important roles in inflammatory disorders such as rheumatoid arthritis (RA), psoriatic arthritis, Crohn's disease, psoriasis, and ankylosing spondylitis (AS). In RA, for example, TNF perpetuates synovial inflammation and promotes bone and cartilage destruction.

Various biologic agents have been developed to inhibit TNF, with the goals of preventing TNF-mediated cellular responses and modulating the activity of other proinflammatory cytokines and processes that are regulated by TNF. Two such agents, etanercept (Enbrel®) and infliximab (Remicade®), are widely used to treat patients with RA.

Etanercept is a soluble human receptor that consists of the Fc portion of IgG1 and the extracellular domain of 2 p75 TNF receptors. Etanercept is currently approved in Canada for the treatment of patients with RA, psoriatic arthritis, and juvenile RA. In the United States, etanercept is approved for the treatment of RA, juvenile RA, psoriatic arthritis, and AS.

Infliximab is a chimeric monoclonal antibody to TNF that is composed of human constant and murine variable regions of IgG1. Infliximab has been approved in both Canada and the United States for the treatment of Crohn's disease and, in combination with methotrexate (MTX), for the treatment of RA.

Although etanercept and infliximab both target TNF, a growing body of evidence highlights differences not only in structure, but also in binding, pharmacokinetics, immunogenicity, and mechanisms of action. The observations suggest that patients who do not respond to or cannot tolerate one TNF inhibitor may respond to another. The current study, also known as the Biologic Observational Switchover Survey (BOSS), monitored efficacy and serious adverse events in patients with RA who switched from infliximab to etanercept treatment in an open label 12-week design.

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Supported by Immunex Corporation, a wholly owned subsidiary of Amgen Inc. (Thousand Oaks, CA, USA), and by Wyeth Pharmaceuticals (Markham, ON, Canada).

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Submitted November 13, 2003; revision accepted July 29, 2004.

MATERIALS AND METHODS

Patients. Patients were eligible if they were at least 18 years of age; met the 1987 American College of Rheumatology (ACR) criteria for RA[1]; had active RA defined as ≥ 3 tender joints and ≥ 3 swollen joints; had no active infections; and were receiving but were to discontinue infliximab infusions. Patients had been treated with standard dosages of infliximab as prescribed by their physicians, and at least 4 weeks but no more than 10 weeks were to have elapsed between the last infliximab infusion and the first etanercept administration. Patients could receive concomitant MTX, corticosteroids, nonsteroidal antiinflammatory drugs (NSAID), and disease-modifying antirheumatic drugs (DMARD) both before and during the study. No instructions were given regarding dose alterations of concomitant RA medication during the study.

Study design. This prospective, 12-week, single-arm, open label, observational study was conducted at 10 sites in Canada. The institutional review boards or ethics committees of all participating centers approved the protocol, and patients gave written informed consent before any study related procedures were performed. Patients self-administered commercially available etanercept for 12 weeks as prescribed by their physicians (twice weekly subcutaneous injections of 25 mg). Concomitant medication remained stable throughout the study for most patients.

Evaluations. Baseline assessments included evaluations of disease severity, concomitant medications, and serum concentrations of antibodies against infliximab (measured using an enzyme immunoassay; Prometheus Laboratories, San Diego, CA, USA). Serious adverse events and usage of concomitant medications were monitored during the study.

The ACR response criteria were assessed at baseline and at Weeks 6 and 12. Individual components of the ACR response criteria included tender joint count (28 joints assessed), swollen joint count (28 joints assessed), patient assessment of pain (scale of 0 to 100), patient and physician global assessments of disease activity (scales of 0 to 10), C-reactive protein (CRP) concentration, and patient assessment of physical function [Health Assessment Questionnaire (HAQ) disability index]. A minimal clinically important difference (MCID) in physical function was defined as a change of at least 0.22 in HAQ score[2].

Statistical analysis. Data were summarized descriptively. For categorical variables, the number and percentage of each category within an assessment were calculated for non-missing data. For continuous variables, the mean, standard deviation, median, and minimum and maximum values were calculated. No inferential analyses were done and no imputation was performed for missing data.

RESULTS

Patients. Of the 25 patients who entered the study, 22 (88%) completed 12 weeks of etanercept treatment. One patient was withdrawn due to noncompliance, one voluntarily withdrew after 6 weeks, and one was withdrawn because of early closure of a study site.

Baseline characteristics of the patients are shown in Table 1. Patients had been treated with infliximab for a mean duration of 15 months; the mean dose at the time of discontinuation was 4.4 mg/kg and the mean frequency was every 7 weeks. Nineteen of the 25 patients (76%) had discontinued infliximab therapy because of lack of efficacy, as judged by the investigator, and 3 others (12%) discontinued because of safety issues (2 due to allergic reactions, 1 due to hair loss). Three patients were allowed to enter the study although 12 to 15 weeks had elapsed since their last infusions of infliximab. At baseline, 48% of patients tested positive for antibodies to infliximab, 24% were negative, and 28% were indeterminate. The mean (median) tender and swollen joint counts were 10.0 (7) and 8.6 (8), respectively. Disease severity, determined by investigators based on patients' clinical presentation, was estimated to be moderate in 14 patients (56%) and severe in 6 patients (24%).

Table 1. Characteristics of patients at baseline.

Characteristic	(n = 25)
Female (%)	21 (84)
White (%)	18 (72)
Mean age, yrs (range)	50.0 (22 to 74)
Mean duration of RA, yrs (range)	10.8 (2 to 36)
Rheumatoid factor positive, (%)*	14 (70)
Mean (median) tender joint count (0–28 joints)	10.0 (7)
Mean (median) swollen joint count (0–28 joints)	8.6 (8)
Mean number of prior DMARD (range)	4.8 (2 to 11)
Prior infliximab therapy	
Mean duration of therapy, mos (range)	15.7 (6 to 22)
Mean dose at the time of discontinuation, mg/kg (range)	4.4 (3 to 8)
Mean frequency of administration, wks (range)	7 (4 to 8)
Concomitant antirheumatic therapies at baseline (%)	
MTX	22 (88)
Oral corticosteroids	12 (48)
None	1 (4)

DMARD: disease-modifying antirheumatic drug. * Data were unavailable for 5 patients.

Concomitant medications. Twenty-four of the 25 patients were taking NSAID or other concomitant antirheumatic medications at baseline. The most common concomitant medication was MTX, used by 22 patients (88%) while taking infliximab and the dose remained unchanged at baseline; individual doses ranged from 7.5 to 25 mg/wk. Oral corticosteroids were used by 12 patients (48%) at baseline. Individual doses ranged from 2.5 to 20 mg/day.

MTX dose was tapered in 2 patients, decreasing from 22.5 and 25.0 mg/wk at baseline, to 17.5 and 12.0 mg/wk, respectively, at Week 6. By Week 12, both these patients had discontinued MTX completely. Corticosteroid dose was tapered in 3 other patients. Two patients received a reduced dose of corticosteroids by Week 12 compared with baseline. One patient discontinued corticosteroids completely by Week 6.

Safety and efficacy. No serious adverse events occurred during the study and no patient withdrew due to adverse events.

Fifty percent of patients achieved an ACR20 at Week 6, and the proportion increased to 64% at Week 12 (Table 2). The proportions of patients achieving ACR50 and ACR70 responses at 6 weeks were 25% and 13%, respectively; similar results were observed at Week 12. Improvements were observed in the mean values of all individual measures of disease activity (Table 3). Clinically meaningful improvements in functional status were experienced by 37% of patients at Week 6 and 59% at Week 12 (Table 2). Improvements in activities of daily living were observed across all 8 HAQ subdomains (dressing and grooming, aris-

Table 2. Improvements in clinical responses and physical function. Values are the number (%) of patients.

	Week 6 (n = 24)	Week 12 (n = 22)
Patients achieving		
ACR20	12 (50)	14 (64)
ACR50	6 (25)	5 (23)
ACR70	3 (13)	1 (5)
Patients achieving		
HAQ improvement of ≥ 1 × MCID	9 (37)	13 (59)
HAQ improvement of ≥ 2 × MCID	7 (29)	10 (45)

ACR20, ACR50, and ACR70: the American College of Rheumatology 20%, 50%, and 70% criteria for improvement, respectively; HAQ: Health Assessment Questionnaire; MCID: minimal clinically important difference, defined as an improvement of ≥ 0.22 in HAQ score.

ing, eating, walking, hygiene, reach, grip, and other activities).

DISCUSSION

Our study evaluated 25 patients with RA who discontinued taking infliximab and were subsequently treated with etanercept. Eighty-eight percent of the patients discontinued infliximab due to lack of efficacy (76%) or safety issues (12%). During the 12-week study, no patients were withdrawn from etanercept due to adverse events or lack of efficacy and no serious adverse events were observed.

Consistent with the results of previous studies[3], patients showed rapid improvements in RA signs and symptoms during etanercept treatment. The proportions of patients achieving ACR50 and ACR70 responses were slightly lower than those observed in some other studies[3], possibly due to the effect of prior and/or ongoing albeit tapering therapy with other antirheumatic drugs that were permitted in this observational study, as well as inclusion criteria that allowed entry of patients with milder disease compared with previous studies. However, ACR20 responses were comparable to those reported in the product labeling for etanercept (59% to 72%). By Week 12, 64% of patients in this study achieved an ACR20 response. Further, 59% experienced clinically meaningful improvements in physical function.

Our results are consistent with those of prior reports describing a total of 39 patients who had switched from infliximab to etanercept[4-8]. Although methodology varied among these studies, about 70% of the patients were reported to have regained clinical responses to etanercept. Additionally, etanercept treatment appeared to be safe in patients previously treated with infliximab, including 1 patient with a history of tuberculosis (controlled with isoniazid) who was treated with etanercept for 1 year with no apparent side effects or pulmonary symptoms[5]. These studies also described the results for a total of 21 patients who switched from etanercept to infliximab. The proportion of patients who responded to treatment with infliximab after discontinuing etanercept was similar to that observed in patients who switched from infliximab to etanercept.

Despite their common ability to inhibit TNF activity, the distinctions between etanercept and infliximab are becoming more broadly appreciated. In addition to differences in structure and dosing, differences in binding, pharmacokinetics, immunogenicity, mechanisms of action, and cost have been reported.

Both etanercept and infliximab bind with high affinity to soluble and cell-associated TNF, but only etanercept binds to lymphotoxin-alpha (previously known as TNF-beta). Binding of infliximab to cells expressing transmembrane TNF can lead to lysis both *in vitro* and *in vivo*, but etanercept does not lyse cells expressing TNF in the presence or the absence of complement[9,10]. This may explain, in part, the different safety profiles of etanercept and infliximab and the ability of one TNF blocker to be effective despite failure of the other.

The half-life of etanercept is about 3 to 5.5 days, whereas that of infliximab is 8 to 9.5 days[3,11]. When infliximab is administered at the recommended maintenance dosage of 3 mg/kg every 8 weeks, high peak serum concentrations are followed by trough levels of infliximab that are undetectable in some patients. Lower trough serum concentrations have

Table 3. Mean values of individual measures of disease activity over time. Scores are measured on a 0–10 scale (best-worst).

	Baseline (n = 25)	Week 6 (n = 24)	Week 12 (n = 22)
Tender joint count (0–28 joints)	10.0	5.2	4.6
Swollen joint count (0–28 joints)	8.6	6.2	3.9
Physician global assessment score	4.5	3.0	2.2
Pain score	54.8	40.0	36.9*
Patient global assessment score	5.4	3.4	3.5
CRP concentration, mg/l	17.1	11.5	11.4**
HAQ disability index	1.53	1.25	1.08

CRP: C-reactive protein (normal range 0–7.9 mg/l); HAQ: Health Assessment Questionnaire, 0–3 (best-worst).
* n = 21. ** n = 19.

been associated with decreased magnitude of ACR responses and increased radiographic progression in some patients with RA[12]. This could possibly explain the need for dose increases or interval reductions to achieve a satisfactory clinical response in some patients. In contrast, the slow absorption and elimination of etanercept results in relatively consistent serum concentrations. Given the higher doses required over time in some patients treated with infliximab, treatment with etanercept may also prove to be cost-effective.

The immunogenicity of biologic agents raises potential safety and efficacy concerns. Because infliximab contains murine sequences, its administration is associated with formation of anti-chimeric antibodies (HACA). Forty-eight percent of patients in this study tested positive for antibodies against infliximab at baseline, before the switch. HACA may have contributed to loss of efficacy during infliximab therapy. In a study of 125 patients with Crohn's disease, 61% of patients developed antibodies against infliximab, and the development of antibodies was associated with an increased risk of infusion reactions and reduced duration of response to treatment[13].

The proportions of patients who develop antibodies to etanercept or infliximab cannot be directly compared, because different assays are used to assess those serological responses. However, etanercept, a human TNF soluble receptor, does not appear to be highly immunogenic. Non-neutralizing antibodies to etanercept occur in less than 5% of adult patients with RA or psoriatic arthritis, and antibodies to etanercept did not correlate with clinical responses or adverse events[3].

Evidence that etanercept and infliximab have different mechanisms of action has surfaced in studies of other diseases such as AS and Crohn's disease, and the evidence is consistent with our observations of differential clinical responses in some patients with RA. Etanercept and infliximab are both effective in treating AS. However, a recent study showed that *in vitro* secretion of TNF and interferon-gamma by T cells from etanercept-treated patients with AS is upregulated[14]. In contrast, a parallel study using the same methodology showed that secretion of these cytokines is downregulated in infliximab-treated patients[15].

Although both TNF inhibitors are effective therapies for RA and AS, only infliximab has been shown to be effective in treating Crohn's disease. The lack of demonstrated efficacy for etanercept may be due to suboptimal doses in patients with Crohn's disease; dosages higher than 25 mg twice weekly have not been studied. However, recent reports have suggested that the basis for the difference may be the ability of infliximab to bind to and induce apoptosis in monocytes and lamina propria T lymphocytes from patients with Crohn's disease[10,16].

Taken together, the available data highlight differences between etanercept and infliximab, and one or more of these differences may account for the differential responses of some patients to these different therapies. Our results suggest that etanercept, a soluble TNF receptor, may provide a safe and effective treatment option for some patients even when infliximab, a monoclonal antibody to TNF, had been ineffective.

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