The Efficacy of Switching from Etanercept to Infliximab in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To describe the degree of clinical benefit in patients with rheumatoid arthritis (RA) who receive infliximab therapy after lack of efficacy with etanercept.

Methods. In a retrospective study among 6 centers primarily designed to assess the safety of infliximab in combination with leflunomide, a standardized chart review form was used to collect data on 93 patients with RA. During that study, it was noted that some of these patients had switched from etanercept to infliximab. In this study, we compared the response of subjects switching from etanercept to infliximab (n = 20) to that of subjects receiving infliximab with no prior tumor necrosis factor (TNF) therapy (n = 73).

Results. The swollen and tender joint count, patient and physician global assessments, morning stiffness, and C-reactive protein all improved substantially in both groups, with no statistical difference in the degree of benefit between the groups. At the time of chart review, switchers had received a statistically higher dose of infliximab than controls (4.4 vs 3.19 mg/kg; p = 0.006) with a total of 5.7 and 5 infusions, respectively.

Conclusion. In this retrospective study, previous lack of efficacy with etanercept did not predict lack of efficacy with infliximab. Indeed, the degree of clinical improvement was similar in both groups, although switchers were receiving a higher dose of infliximab at the time of chart review. Our findings suggest that clinical response may differ between anti-TNF agents, and lack of response to one agent may not predict a lack of response to another. (J Rheumatol 2004;31:1098–102)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ETANERCEPT INFLIXIMAB EFFICACY TREATMENT

Lack of efficacy or toxicity may limit the use of disease modifying antirheumatic drugs (DMARD) currently used for rheumatoid arthritis (RA). Tumor necrosis factor (TNF) inhibitors represent a class of biologic agents that have gained significant attention for their rapid onset of action and disease modifying abilities. Studies show etanercept, a recombinant TNF-α receptor fusion protein, to be equivalent to methotrexate (MTX) in early RA[1,2]. Infliximab, a chimeric monoclonal IgG-1 antibody against TNF-α, is normally used in combination with MTX for those with an insufficient response to MTX alone[3]. A third TNF inhibitor, adalimumab, is now commercially available. There is little information regarding the clinical benefit of changing from one TNF inhibitor to another, when the first agent has demonstrated lack of efficacy.

A French study described the utility of switching TNF inhibitors among 131 patients with RA receiving either etanercept or infliximab[4]. Eight patients switched from infliximab to etanercept, with 5 reporting improvement in RA symptoms, while 6 switched from etanercept to infliximab with clinical improvement in 3 patients. Our study adds to the existing data by comparing the response of RA patients who switch from etanercept to infliximab with that of patients receiving infliximab with no previous TNF therapy.

MATERIALS AND METHODS

In this multicenter retrospective study performed to evaluate the safety of infliximab in combination with leflunomide, all subjects were required to be taking the combination of these 2 DMARD at study entry[5]. A standardized chart review form was used to collect data on demographics, markers of RA severity, and adverse events noted during the use of combination therapy. Demographic data included age, sex, rheumatoid factor results, the

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presence of erosions or joint space narrowing by standard radiographs, functional class, and disease duration. Current DMARD (aside from infliximab and leflunomide) and previous DMARD were recorded along with the indication for discontinuation, if known.

The clinical benefit of infliximab in subjects with previous use of etanercept (referred to as "switchers") was compared to the efficacy of infliximab in subjects receiving no previous TNF inhibitors ("controls"). The onset of infliximab therapy was recorded along with the dose and total number of infusions. The frequency and indication for dose reduction and temporary or permanent discontinuation of infliximab was also noted[5].

Efficacy measures included tender and swollen joint counts (28 joint count), morning stiffness (minutes), dose of prednisone, Westergren sedimentation rate, and C-reactive protein (CRP). Subjective data on patient and physician global assessments were also available (rated as very poor, poor, fair, good, and very good). Pain scores were inconsistently recorded, preventing adequate analysis. The efficacy measures for the time point prior to starting infliximab (taking etanercept, n = 20; taking other DMARD, n = 73) were compared to the efficacy measures after initiation of infliximab therapy. Since the practice of the investigators was to switch from etanercept to infliximab with no specific washout period, efficacy measures for switchers were obtained while they used etanercept.

Safety measures included laboratory data (complete blood count, AST, ALT, albumin, and creatinine) before (taking etanercept) and after the switch to infliximab therapy, number and severity of infusion reactions, infections, hospitalizations, other side effects, and death.

For analysis, subjects were divided into 2 groups: switchers and controls. The 2 groups were compared based on changes (pre-infliximab vs post-infliximab) in disease control, laboratory values, and other safety indicators. Comparisons of change in continuous and ordinal outcomes were based on the Wilcoxon rank-sum test. Comparisons of rates of adverse outcomes were based on Fisher's exact test.

RESULTS

Patient characteristics. Twenty patients who switched from etanercept to infliximab (switchers) were compared with 73 patients starting infliximab with no previous anti-TNF therapy (controls). Baseline characteristics of the 2 groups were similar (Table 1). Previous DMARD are summarized in Table 2, with no statistical difference in the form of DMARD between the 2 groups. However, the mean number of previous DMARD was significantly higher in switchers compared to controls (4.3 and 2.5, respectively; $p < 0.0001$). If previous use of etanercept was excluded, the mean number of previous DMARD was still statistically higher in switchers ($p = 0.010$).

Of the 20 patients who discontinued etanercept therapy, 17 discontinued due to lack of efficacy. Among 3 other patients, one stopped etanercept due to a shortage of the drug, and another due to patient concerns about safety of the drug. A final patient discontinued etanercept due to thrombocytopenia (platelet count 101,000/µl) while under MTX/etanercept combination therapy that persisted with leflunomide and infliximab. Other mild adverse events that occurred during etanercept therapy were nausea, vomiting, diarrhea, and herpes zoster.

All 93 patients in this study were taking infliximab in combination with leflunomide, since the original study focused primarily on the safety of these 2 drugs when used in combination. In all but 3 patients, leflunomide had been taken for several months and infliximab was added later, with a mean duration of leflunomide therapy of 18 ± 9 months (range 3–32 mo, median 18.5 mo). At the time of chart review, controls had received an average of 5 infliximab infusions with a mean dose of 3.19 mg/kg, while switchers were given an average of 5.7 infliximab infusions with a mean dose of 4.4 mg/kg ($p = 0.006$ for the difference in mg/kg dose).

Four switchers (20%) were also taking additional DMARD during the study, including azathioprine (n = 1), sulfasalazine (n = 1), and MTX (n = 2). Concomitant DMARD were noted in 4 controls (5.4%), including MTX (n = 3) and hydroxychloroquine (n = 1). Use of prednisone was noted in 13 switchers (mean dose 8.5 mg daily) and 37 controls (mean dose 4.3 mg daily).

Efficacy of switching. Partial data on drug efficacy were available for all 93 subjects in this retrospective chart review, with no difference in the degree of missing data between groups except for patient global assessment (avail-

Table 1. Demographic details of subjects.

	Switchers, n = 20	Controls, n = 73	p
Average age, yrs	48	54	0.14
Female, n (%)	12 (60)	55 (75)	0.28
Average duration of disease, mo	111	129	0.79
Seropositive, n (%)	13 (65)	58 (79)	0.29
Radiographic findings, n (%)			
Erosions	11 (55)	38 (52)	0.98
Periarticular osteopenia	11 (55)	39 (53)	0.90
Joint space narrowing	9 (45)	49 (67)	0.12
Functional class, n (%)	n = 20	n = 66	
Class I	5 (25)	16 (24)	
Class II	8 (40)	29 (44)	
Class III	6 (30)	18 (27)	
Class IV	1 (5)	3 (5)	

p = 0.99 for differences in functional class.

Table 2. Summary of previous DMARD use and indication for discontinuation.

DMARD	Switchers, n = 20	Controls, n = 73	p
Gold (%)	n = 10 (50) LOE = 6 AE = 5	n = 34 (47) LOE = 20 AE = 7	0.98
Hydroxychloroquine (%)	n = 15 (75) LOE = 11 AE = 4	n = 35 (48) LOE = 23 AE = 4	0.058
Methotrexate (%)	n = 20 (100) LOE = 10 AE = 8	n = 66 (90) LOE = 36 AE = 22	0.34
Sulfasalazine (%)	n = 11 (55) LOE = 6 AE = 2	n = 26 (36) LOE = 14 AE = 5	0.19
Other (%)	n = 11 (55) Azathioprine = 3 Cyclosporine = 3 Drug studies = 2 Tetracyclines = 3	n = 24 (33) Azathioprine = 6 Cyclophosphamide = 2 Cyclosporine = 6 D-penicillamine = 4 Drug studies = 4 Mycophenolate = 1 Tetracycline = 1	0.12

LOE: lack of efficacy; AE: adverse event, as the indication for discontinuation of prior DMARD. One subject stopped gold for both LOE and an AE.

able for 80% of switchers and 38% of controls; p = 0.0023). Prior to infliximab therapy, both groups had active RA, with a mean of 13–14 swollen and tender joints, elevated CRP, prolonged morning stiffness, and patient and physician global assessments that were predominantly "very poor" or "poor" (Table 3).

Table 3. Comparison of disease control in subjects with and without previous use of etanercept, who then received infliximab.

	Switchers, n = 20				Controls, n = 73			
	Taking Etanercept	After Infliximab	Improvement, %		Before TNF Inhibitors	After Infliximab	Improvement, %	Comparison Between Groups, p
Swollen joint count, n = 17	14	5	64	Swollen joint count, n = 56	13	5	62	0.56
Tender joint count, n = 16	14	4	71	Tender joint count, n = 56	14	6	57	0.42
Patient global assessment, n = 16	Very poor = 1 Poor = 10 Fair = 0 Good = 1 Very good = 0	Very poor = 0 Poor = 2 Fair = 5 Good = 2 Very good = 3	Trend to improvement	Patient global assessment, n = 28	Very poor = 1 Poor = 21 Fair = 6 Good = 0 Very good = 0	Very poor = 1 Poor = 2 Fair = 9 Good = 7 Very good = 9	Trend to improvement	0.88
Physician global assessment, n = 13	Very poor = 0 Poor = 12 Fair = 1 Good = 0 Very good = 0	Very poor = 0 Poor = 3 Fair = 4 Good = 3 Very good = 3	Trend to improvement	Physician global assessment, n = 28	Very poor = 2 Poor = 24 Fair = 2	Very poor = 1 Poor = 2 Fair = 6 Good = 13 Very good = 6	Trend to improvement	0.069
Prednisone dose, mg/day, n = 13 of 20	8.5	4	53	Prednisone dose, mg/day, n = 37 of 66	4.3	2.9	33	0.078
ESR, mm/h, n = 11	13	26	Increased by 100%	ESR, mm/h, n = 40	45	28	38	0.035
CRP, mg, n = 6	23.8	17.1	28	CRP, mg, n = 29	11.5	5.6	51	0.46
Morning stiffness, min, n = 10	180	120	33	Morning stiffness, min, n = 41	67	27	60	0.53

"n" in the left column indicates the number of subjects for which each variable was recorded.

After onset of infliximab therapy, both groups experienced a clinically significant improvement in disease measures including tender and swollen joint counts, patient and physician global assessment, CRP, and morning stiffness (Table 3). Comparing switchers and controls, these disease measures improved in a similar fashion, with no statistically significant difference between the groups by Wilcoxon rank-sum test. The reduction in prednisone dose was also similar between the groups. The sedimentation rate was the only disease measure that was significantly different between groups, due to 3 switchers who had an increase in sedimentation rate during the study.

Toxicity. Safety monitoring variables included laboratory testing, rates of infections, and infusion reactions. Laboratory measures (complete blood count and liver function tests), performed at the discretion of the treating physician during the duration of combination therapy with leflunomide and infliximab, identified no evidence of hematological or hepatic toxicity in either group of patients (data not shown). Ten infections occurred during anti-TNF therapy, with 3 infections in switchers and 7 infections in controls (15% and 9.6%, respectively; p = 0.69 for the difference between groups by Fisher's exact test).

Five infections resolved with outpatient antibiotic therapy. Hospitalization for treatment of infection was necessary in one switcher with a septic joint and 4 of the control patients (p = nonsignificant, Fisher's exact test for differences in rates of admission between groups). Infections in control patients included cellulitis (n = 1), foot infection (n = 1), and bacterial pneumonia (n = 2). One patient developed bacterial pneumonia in the setting of rheumatoid lung disease and subsequently succumbed to adult respiratory distress syndrome (ARDS).

Infliximab was discontinued for lack of efficacy in 2 switchers and 2 controls[5]. One switcher stopped infliximab due to rash and nausea. Five controls also stopped infliximab for rash (n = 2, one of whom reported increasing arthralgia), lung cancer (n = 1), pneumonia/acute respiratory distress syndrome (n = 1), and cellulitis, leg edema, and newly diagnosed colon cancer (n = 1).

The patient with lung cancer was a life-long smoker who was diagnosed with lung cancer at age 60 after receipt of 4 infliximab infusions. This information was discovered when the patient did not return to clinic and was contacted by telephone; the cell type of lung cancer is unknown and the patient was lost to followup. The patient with ARDS had underlying rheumatoid lung disease and, after exposure to a child with a bacterial infection, developed severe pneumonia and died of ARDS at age 60, after receiving a total of 3 infliximab infusions. Colon cancer was diagnosed in one patient after a single infliximab infusion.

Infusion reactions occurred in 4 of 479 infusions (0.8%), and were limited to the control group (p = 0.58, Fisher's exact test for difference in infusion reactions between the groups). None of these infusion reactions involved cardiac or respiratory compromise. There were no statistically significant differences in rates of infection, hospital admission, or infusion reactions between switchers and controls.

DISCUSSION

In this small retrospective study, we observed that patients with RA who do not respond fully to etanercept may experience improved disease control with a switch to infliximab. The efficacy of infliximab was clinically and statistically similar in subjects who had previously taken etanercept, compared to those who had never received anti-TNF therapy; indeed both groups experienced a significant improvement in disease activity. The exception was an increase in the Westergren sedimentation rate in switchers, accounted for by 3 subjects who had an increase in sedimentation rate.

The mean dose of infliximab was statistically higher in switchers compared to controls, suggesting that a higher dose of infliximab may be necessary to achieve disease control in subjects who experience previous lack of efficacy taking etanercept. Importantly, there were no differences in rates of adverse events with infliximab, including infusion reactions, implying that the safety of infliximab therapy is not influenced by previous use of etanercept.

A weakness of this study is its retrospective design, leading to lack of disease stratification at baseline, and incomplete data on all drug efficacy measures for each subject. However, partial data were available for each patient and are therefore included in this report; statistical analysis shows no difference in the degree of missing data between the 2 groups except for the patient global assessment. At baseline, both switchers and controls had similar disease activity, but switchers had received a higher number of previous DMARD, potentially making this group less likely to respond to new therapies[6]. Another potential weakness of the study is the use of concomitant DMARD. Although only 8 patients (8.6%) were taking DMARD other than infliximab and leflunomide, a higher number of switchers than controls were taking additional DMARD, potentially biasing this group to respond better. In addition, the small number of patients in each group could result in a lower power, or ability to detect differences in the efficacy of infliximab between groups. As well, this study provides only short-term data on the response to infliximab, and does not assess whether patients experiencing previous anti-TNF treatment failure will manifest a less robust longterm response to the drug, or require higher doses to achieve full benefits. Finally, although the investigators prescribed etanercept for at least 3 months before determining lack of efficacy for an individual with RA, the study does not provide specific data on whether the lack of efficacy to etanercept occurred after several months of benefit, or after an initial 3-month trial.

In this retrospective study, previous lack of efficacy with etanercept did not predict a lack of efficacy with infliximab. Indeed, the degree of clinical improvement was similar in the anti-TNF naive group and those with previous lack of efficacy taking etanercept. One other study has reported the benefit of switching from one TNF inhibitor to another, among 131 patients with RA taking etanercept or infliximab[4]. In that French study, 8 of 67 patients receiving infliximab switched to etanercept, with clinical improvement in 5 patients, no response in 2, and one patient who stopped therapy for personal reasons. Among 64 patients receiving etanercept, 6 switched to infliximab, with clinical benefit in 3, no response in 2, and an adverse event in one patient. From this study and our own experience, we infer that lack of efficacy to one anti-TNF agent does not predict lack of response to another TNF inhibitor.

The observation that lack of efficacy with one TNF inhibitor does not preclude benefit with another suggests that the immune effects of etanercept and infliximab may differ in a given individual. A better understanding of this concept may prove valuable, as 3 anti-TNF therapies are commercially available for treatment of RA. Research is needed to define the patient characteristics that predict a response to different TNF inhibitors, such as pharmacokinetics, TNF polymorphisms, cytokine profiles, and disease measures. We hope the results from this retrospective study will spur prospective research evaluating the efficacy, and predictors of efficacy, when switching from one TNF inhibitor to another.

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