Do the Clinical Responses and Complications Following Etanercept or Infliximab Therapy Predict Similar Outcomes with the Other Tumor Necrosis Factor-α Antagonists in Patients with Rheumatoid Arthritis?

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ABSTRACT. ***Objective.*** To study a group of 29 patients with rheumatoid arthritis (RA) who have been treated with both tumor necrosis factor (TNF)-α antagonists, etanercept and infliximab and to determine the correlation of responses and complications seen in these patients.

Methods. Patients' responses to and complications from either treatment were reviewed retrospectively by determining the joint counts, acute phase reactants, as well as occurrences of infection, hypersensitivity, and cytopenia. The correlation of responses and complications was determined using phi coefficients and exact p values.

Results. There was no correlation between the joint count responses (exact p value for correlation coefficient, 0.70) and acute phase reactant responses (exact p value 0.14) with the use of etanercept and infliximab in the same patient. There was no correlation between the occurrences of drug hypersensitivity reactions (exact p value 0.20) or infectious complications (exact p value 1.00). However, the occurrence of anemia with the use of one TNF-alpha antagonist was correlated with a similar occurrence with the use of the other antagonist (exact p value 0.007).

Conclusion. Our study indicates that patients who fail to respond to one TNF-α antagonist can respond to the other antagonist. Furthermore, there appears to be no contraindication to using one TNF-α antagonist for patients who have developed hypersensitivity reactions to the other. The infections observed in our study were generally mild and did not necessarily recur with the use of the second antagonist. In contrast, anemia, when present with the use of one agent, was likely to occur with the use of the second agent. (J Rheumatol 2003;30:2315–8)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ETANERCEPT INFLIXIMAB CLASS EFFECT

The treatment of rheumatoid arthritis (RA) has changed significantly over the past 3 years with the introduction of new agents such as the tumor necrosis factor (TNF)-α antagonists, etanercept and infliximab. New guidelines for the management of RA have been developed to incorporate these new treatment options[1-3].

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Etanercept is a fusion molecule consisting of two p75 TNF-α receptors and the human IgG1 Fc region. Infliximab is a chimeric monoclonal antibody against TNF-α[4]. Both drugs showed efficacy in achieving significant clinical responses using the American College of Rheumatology (ACR) criteria and in reducing joint destruction[5-8].

In clinical trials, both drugs have been associated with toxicities, particularly infections and hypersensitivity reactions[6,8]. Aplastic anemia, opportunistic infections, and lupus-like illnesses have also been reported by a US Food and Drug Administration arthritis advisory committee[9].

The biologic changes associated with anti-TNF-α therapy have been reviewed[10,11]. Although etanercept and infliximab both neutralize TNF-α, different molecular approaches are used. It is important to determine whether these differences translate into different clinical outcomes. For example, should these agents be considered to have similar class effects, and if so, should the failure to respond or the development of toxicity with one agent preclude the use of the other? To attempt to answer these questions, we

retrospectively studied 29 patients who have been treated with both etanercept and infliximab to determine whether there were any correlations between the clinical responses and toxicities seen with these agents.

MATERIALS AND METHODS

Patients who were diagnosed RA and who have been treated with both etanercept and infliximab at the Brigham and Women's Hospital between January 2000 and June 2001 were identified by record review with the approval of the Institutional Review Board of the hospital. Twenty-nine such patients were identified after a review of 142 records. Information was obtained regarding demographics, disease variables, prior treatments, and reasons for starting and terminating either TNF-α antagonist. Responses and complications to these agents were reviewed up to the end of the treatment, and if still in use, to the date of the review. The average duration of observed treatment for etanercept was 8.2 months and for infliximab, 10 months. Changes in the joint counts and acute phase reactants [erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)] were used to assess responses. The numerical changes in joint count and acute phase reactant were converted to > 20% responses and < 20% responses, and the concordant and discordant cases were summarized in the 2 × 2 contingency tables. Concordant and discordant cases of infection, hypersensitivity, and anemia were also summarized using 2 × 2 contingency tables.

We determined the correlation of responses and complications using phi correlation coefficient for the joint counts, acute phase reactants, cytopenias, infections, and hypersensitivity reactions. Both approximate p values and p values from exact test (for small samples) were determined, but the final conclusions were based on the p values from the exact test. Hypothesis testing for significance used p values < 0.05 (2-tailed), and the SPSS statistical package (SPSS Inc, Chicago, IL) was used for statistical computations.

RESULTS

The characteristics of the study population are shown in Table 1. Etanercept was the first TNF-α antagonist used in 24 patients, while infliximab was the first antagonist used in 5 patients. Methotrexate was the last disease modifying antirheumatic drug (DMARD) used prior to anti-TNF-α therapy in 62% of patients, while leflunomide was the last DMARD used in 31% of patients. While taking etanercept (whether as first or second antagonist), 16 of 29 patients were also using DMARD. While taking infliximab, 22 of 29 patients were also using DMARD. Of the 24 patients who used etanercept before infliximab, 12 changed because of inadequate response, 10 because of toxicity. Of the 5 patients who used infliximab before etanercept, 2 changed because of inadequate response, 3 because of toxicity. At the end of the study, 31% of patients were no longer treated with TNF-α antagonists, while 69% were maintained on this therapy.

Table 2 describes the joint count and acute phase reactant responses to both agents. The responses of these clinical variables to etanercept did not correlate with the development of similar responses to infliximab in the same patients.

Table 3 describes the adverse effects of infection, hypersensitivity, and anemia with either treatment. There were no correlations of infectious and hypersensitivity complications, but there was significant correlation (exact p 0.007) of anemia from the use of the 2 anti-TNF-α therapies.

Table 1. Characteristics of the study population.

	Patients, n	%
Age	29	100
20–40	3	10.4
40–60	11	37.9
60–90	15	51.7
Gender	29	100
Male	3	10.4
Female	26	89.6
Duration of disease	29	100
0–5 yr	2	6.9
6–10 yr	3	10.4
> 10 yr	14	48.3
Unknown	10	34.4
Rheumatoid factor	29	100
Positive	10	34.4
Negative	6	20.8
Unknown	13	44.8
Rheumatoid nodule	29	100
Positive	9	31.1
Negative	15	51.7
Unknown	5	17.2
DMARD Used Over Past 10 Years, n	29	100
0–2	10	34.4
3–5	15	51.7
> 5	4	13.9
First TNF-α antagonist used		
Etanercept	24	100
Reason for change to Infliximab		
Inadequate response	12	50
Toxicity	10	41.7
Other*	2	8.3
Infliximab	5	100
Reason for change to etanercept		
Inadequate response	2	40
Toxicity	3	60

* One patient did not wish to continue needle injection after a period of trial; one patient completed free drug study of etanercept.

DISCUSSION

Although etanercept and infliximab both neutralize TNF-α, they use different molecular approaches. In one study of 17 patients with an inadequate response to etanercept, 16 (94%) showed a response to infliximab in terms of improvement in the painful/swollen joint count and the ESR[12]. However, another study that compared etanercept-naïve versus etanercept-failure patients who subsequently received infliximab found that only 3 out of 21 (14%) etanercept-failure patients responded to infliximab[13].

Our study showed no correlation between the responses to the 2 TNF-α antagonists in terms of joint counts and acute phase reactants. This suggests that patients who fail etanercept can be treated successfully with infliximab and *vice versa*. This may be due to molecular differences between the 2 agents such as differences in induction of neutralizing antibodies[8], cell lysis with surface-bound TNF-α[4], lymphotoxin inhibition[14], or binding affinity to TNF-α[15].

Table 2. Test of correlation of joint count response and acute phase reactant (APR) response to etanercept and infliximab.

		Infliximab Joint Count Response		Total			
		< 20%	> 20%		Phi Coefficient		
Etanercept joint count response	< 20%*	7	7	14	Value	App p	Exact p
	> 20%**	5	9	14	0.144338	0.445009	0.703567
Total		12	16	28			
		Infliximab APR Response		Total			
		< 20%	> 20%		Phi Coefficient		
Etanercept APR response	< 20%*	5	9	14	Value	App p	Exact p
	> 20%**	5	1	6	–0.436436	0.050962	0.140867
Total		10	10	20			

* < 20% decrease, or any increase, in tender/swollen joints or acute phase reactants; ** > 20% decrease in tender/swollen joints or acute phase reactants; App: approximate.

Table 3. Test of Correlation of complications from etanercept and infliximab.

		Infection With Infliximab*		Total			
		No	Yes		Phi Coefficient		
Infection with etanercept**	No	18	6	24	Value	App p	Exact p
	Yes	4	1	5	–0.044137	0.812126	1
Total		22	7	29			
		Hypersensitivity With Infliximab†		Total			
		No	Yes		Phi Coefficient		
Hypersensitivity with etanercept‡	No	12	10	22	Value	App p	Exact p
	Yes	6	1	7	–0.274883	0.138795	0.202053
Total		18	11	29			
		Anemia With Infliximab		Total			
		No	Yes		Phi Coefficient		
Anemia with etanercept	No	21	0	21	Value	App p	Exact p
	Yes	3	3	6	0.661438	0.000588	0.006838
Total		24	3	27			

* 1 bronchitis, 1 sinusitis, 2 pneumonia, 2 cellulitis, 1 fungal esophagitis; ** 3 bronchitis, 1 sinusitis, 1 cellulitis; † 1 flushing, 3 urticaria, 1 facial edema, 5 rash, 1 chest pain; ‡ 4 urticaria, 3 rash. App: approximate.

Our study found a correlation between the occurrence of anemia with the use of either etanercept or infliximab. Although pancytopenia and aplastic anemia have been described with etanercept, these toxicities were not observed in our patients. There were 9 cases of anemia. All but 2 cases showed decline in hemoglobin from the baseline value at the start of treatment. In one of these 2 cases, there was also decline in the first few weeks but hemoglobin subsequently improved. In the other case, there was concomitant iron-deficient anemia that confounded the observation. When this case was excluded from statistical analysis, the correlation was still significant (exact p 0.03). Two cases of leukopenia also developed with etanercept treatment, but none occurred with infliximab.

In our study, there were 5 infections in 238 patient-months of observation with etanercept therapy, compared to 7 infections in 294 patient-months with infliximab therapy. Most of the infections we observed were mild in nature. There was no correlation between the infectious complications with the use of either TNF-α antagonist. This suggests there is no contraindication to using a second TNF-α antagonist when a non-serious infection has occurred with the first agent.

Our study also found no correlation between the development of hypersensitivity complications with either therapy. This suggests that the development of such a reaction with one agent does not predict a similar reaction to the other. This is clinically important because in our study, most of the drug terminations were due to hypersensitivity reactions.

In conclusion, our findings suggest a lack of correlation between the clinical responses or development of adverse effects when etanercept and infliximab were used in the same patients. The failure to respond to one agent does not preclude the use of the other. Similarly, the development of non life-threatening infections or hypersensitivity reactions with one agent is not a contraindication to using the second agent.

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REFERENCES

1. ACR Subcommittee on RA Guidelines. Guidelines for the management of rheumatoid arthritis, 2002 update. Arthritis Rheum 2002;46:328-46.
2. Furst DE, Keystone EC, Breedveld FC, et al. Updated consensus statement on tumour necrosis factor blocking agents for the treatment of rheumatoid arthritis and other rheumatic diseases (April 2001). Ann Rheum Dis 2001;60 Suppl 3:2-5.
3. Emery P, Reginster JY, Appelboom T, et al. WHO collaborating centre consensus meeting on anti-cytokine therapy in rheumatoid arthritis. Rheumatology 2001;40:699-702.
4. Keystone EC. Tumor necrosis factor-alpha blockade in the treatment of rheumatoid arthritis. Rheum Dis Clin North Am 2001;27:427-43.
5. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999;130:478-86.
6. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000;343:1586-93.
7. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340:253-9.
8. Lipsky PE, van der Heijde DM, St Clair EW, et al; Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000;343:1594-602.
9. Cush JJ, Matteson EL. FDA Advisory committee reviews safety of TNF inhibitors. Hotline American College of Rheumatology; Sept, 2001 [cited June 13, 2003]. Available from: http://www.rheumatology.org/research/hotline/0901tnf.html
10. McInnes IB. Rheumatoid arthritis. From bench to bedside. Rheum Dis Clin North Am 2001;27:373-87.
11. Maini RN, Taylor PC, Plaeolog E, et al. Anti-tumour necrosis factor specific antibody (infliximab) treatment provides insights into the pathophysiology of rheumatoid arthritis. Ann Rheum Dis 1999;58 Suppl 1:I56-60.
12. Shergy WJ, Phillips Jr RM, Hunt RE, Hernandez J. Safety and efficacy of infliximab therapy after etanercept failure: a case series [abstract]. Arthritis Rheum 2001;44 Suppl 9:S81.
13. Yazici Y, Erkan D, Leff L, Kulman I, Harrison MJ, Schwartzman S. Do etanercept (ETA) naïve patients respond better to infliximab (INF) than RA patients who have failed ETA? [abstract]. Arthritis Rheum 2001;44 Suppl 9:S81.
14. Kremer JM. Rational use of new and existing disease-modifying agents in rheumatoid arthritis. Ann Intern Med 2001;134:695-706.
15. Scallon B, Cai A, Solowski N, et al. Binding and functional comparisons of two types of tumor necrosis factor antagonists. J Pharmacol Exp Ther 2002;301:418-26.