Randomized, Double-Blind, Placebo-Controlled, Pilot Trial of Infliximab, a Chimeric Monoclonal Antibody to Tumor Necrosis Factor-α, in Patients With Moderate-to-Severe Heart Failure

Results of the Anti-TNF Therapy Against Congestive Heart failure (ATTACH) Trial

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Background—Preclinical and preliminary clinical data have suggested that tumor necrosis factor-α (TNFα) may play a role in the evolution and progression of heart failure and that inhibition of TNFα may favorably modify the course of the disease. We evaluated the efficacy and safety of infliximab, a chimeric monoclonal antibody to TNFα, in patients with moderate-to-severe heart failure.

Methods and Results—One hundred fifty patients with stable New York Heart Association class III or IV heart failure and left ventricular ejection fraction ≤35% were randomly assigned to receive placebo (n=49), infliximab 5 mg/kg (n=50), or infliximab 10 mg/kg (n=51) at 0, 2, and 6 weeks after randomization and were followed-up prospectively for 28 weeks. Neither dose of infliximab improved clinical status at 14 weeks, the primary endpoint of the study, despite suppression of inflammatory markers (C-reactive protein and interleukin-6) and a modest increase in ejection fraction in the patients receiving 5 mg/kg (P=0.013). Furthermore, after 28 weeks, 13, 10, and 20 patients were hospitalized for any reason in the placebo, 5 mg/kg infliximab, and 10 mg/kg infliximab groups, respectively. The combined risk of death from any cause or hospitalization for heart failure through 28 weeks was increased in the patients randomized to 10 mg/kg infliximab (hazard ratio 2.84, 95% confidence interval 1.01 to 7.97; nominal P=0.043).

Conclusions—Short-term TNFα antagonism with infliximab did not improve and high doses (10 mg/kg) adversely affected the clinical condition of patients with moderate-to-severe chronic heart failure. (Circulation. 2003;107:3133-3140.)

Key Words: heart failure proteins antibodies

Serum levels of tumor necrosis factor-α (TNFα) are elevated in patients with heart failure, and the magnitude of the increase is directly correlated with the severity of disease.1,2 TNFα is produced by the failing heart (possibly due to an increase in ventricular wall stress3,4) and may contribute directly to the evolution and progression of heart failure.5 TNFα has established negative inotropic effects,6 and transgenic mice that overproduce myocardial TNFα develop systolic dysfunction.7 In addition, TNFα can cause pathological changes in the myocardium, including ventricular remodeling, interstitial fibrosis, and cardiomyocyte apoptosis.8,9 Changes that are characteristic of those seen in the failing human heart. The hypothesis that TNFα is a deleterious factor in heart failure is further supported by a preliminary clinical study with the TNFα antagonist etanercept (a soluble p75 TNF receptor fusion protein).10 In this pilot trial, treatment with etanercept was reported to improve cardiac function and clinical status in patients with moderate-to-severe symptoms.

Infliximab is a recombinant immunoglobulin G1-κ, human-murine chimeric monoclonal antibody that specifically and potently binds to and neutralizes the soluble TNFα.
Crohn’s disease when conventional therapies are inadequate and for active rheumatoid arthritis that is not responding adequately to methotrexate therapy. The ATTACH (Anti-TNF Therapy Against Congestive Heart failure) trial was designed to evaluate, in a preliminary fashion, whether TNFα inhibition with infliximab could have favorable effects in patients with moderate-to-severe heart failure.

Methods

Study Patients

One hundred fifty patients were enrolled at 32 US study centers between August 14, 2000, and April 20, 2001. Men and women at least 18 years old with stable New York Heart Association (NYHA) class III or IV heart failure associated with a radionuclide left ventricular ejection fraction ≤35% within 14 days before randomization were eligible for enrollment. Heart failure was considered stable if none of the following occurred within 2 weeks before screening: Change in NYHA functional class, hospitalization for heart failure, or administration of any intravenous medication for heart failure. Patients were required to have received treatment with a diuretic and an angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin II receptor blocker if intolerant of ACE inhibitors) for at least 85% of the time during the prior 3 months. β-Blockers, digoxin, and spironolactone were allowed, provided that they were started ≥3 months before screening and were to be continued throughout the 28-week trial period; patients not receiving these medications at the time of screening were not to have received them within 3 months. Treatment with vasodilators or nitrates was permitted but not required. Doses of all cardiac medications were to be constant for at least 2 weeks before and during screening. Patients were required to have received adequate immunization against Streptococcus pneumoniae ≥2 weeks before randomization.

Patients were excluded if they had hemodynamically significant obstructive valvular disease, cor pulmonale, restrictive or hypertrophic cardiomyopathy, constrictive pericarditis, or congenital heart disease; had experienced an acute myocardial infarction or coronary revascularization procedure within 2 months; or were likely to undergo coronary revascularization or heart transplant during the anticipated duration of the study. Patients were not allowed to participate if they had previously been resuscitated from sudden death or had a therapeutic discharge of an implanted implantable cardioverter defibrillator within 3 months or had received within 2 weeks or were likely to receive within the following 28 weeks any of the following: A class IC or III antiarrhythmic other than amiodarone; a calcium channel blocker other than amiodoline for hypertension or angina; a positive inotrope other than digoxin; or a nonsteroidal antiinflammatory drug other than aspirin. In addition, patients were not enrolled if they had experienced a serious infection within 2 months; had latent tuberculosis or had tuberculosis within 3 years; had a documented human immunodeficiency virus infection; or had any other opportunistic infection within 6 months. Finally, patients who within 3 months had been treated with infliximab or other therapeutic agents that could interfere with the actions of TNFα (eg, etanercept, pentoxifylline, thalidomide, or D2E7) were not allowed in the study.

Study Design

Informed consent was obtained from all patients according to institutional review board guidelines. Within 14 days before planned randomization, potential study candidates underwent a screening evaluation, including medical history and physical examination, assessment of NYHA class, routine laboratory tests, chest x-ray, 12-lead ECG, and determination of left ventricular ejection fraction by radionuclide ventriculography. Patients meeting all eligibility criteria underwent a repeat assessment of NYHA class just before randomization to reaffirm eligibility, and a baseline assessment of quality of life using the Minnesota Living With Heart Failure questionnaire was performed. Blood was collected for baseline measurements of inflammatory markers (TNFα, interleukin-6 [IL-6], and C-reactive protein [CRP]). Eligible patients were randomly assigned in a double-blind fashion to receive infliximab 5 mg/kg, infliximab 10 mg/kg (to maximum of 1 g), or placebo immediately after randomization and again at 2 and 6 weeks after randomization. At each of the 3 visits, the study agent was administered as a 2-hour intravenous infusion.

Randomized patients underwent follow-up evaluations at 1, 2, 6, 10, 14, 20, and 28 weeks after randomization, whether the study agent was administered or was prematurely discontinued. At each visit, patients provided an overall assessment of their heart failure status, relative to baseline, using one of the following categories: Unchanged, mildly improved or worse, moderately improved or worse, markedly improved or worse (patient global assessment); NYHA class was assessed; blood samples were drawn for inflammatory markers and serum infliximab concentrations; and patients were queried about the occurrence of adverse effects, hospitalization, and other major clinical events. Repeat assessments of left ventricular ejection fraction and Minnesota Living With Heart Failure score were performed at 14 and 28 weeks after randomization. Every attempt was made to maintain background medication constant throughout the 28-week trial period, and patients were not allowed to receive open-label infliximab or etanercept during this time. The vital status of all patients was assessed at 1 year after randomization.

The primary endpoint of the study was the change in clinical status at 14 weeks. Clinical status was assessed by the clinical composite score, which categorized each patient as improved, worse, or unchanged using prespecified criteria. Patients were considered improved if they showed an improved NYHA class or moderate or marked improvement in the patient global assessment; to be improved, none of the criteria for worse clinical status could be present. Patients were considered worse if they died, were hospitalized for heart failure, or had worsening NYHA class or moderate or marked worsening of the patient global assessment. Patients who were neither improved nor worse were considered to be unchanged.

A patient was considered to have been hospitalized for heart failure if he/she was hospitalized at least overnight for or with worsening heart failure and received intravenous diuretics, vasodilators, or positive inotropic drugs within 24 hours of admission for the treatment of heart failure.

Secondary endpoints included change in inflammatory markers during the 28-week trial period, change in left ventricular ejection fraction at 14 and 28 weeks, the combined risk of death or hospitalization for worsening heart failure at 28 weeks, and the change in Minnesota Living With Heart Failure score at 14 and 28 weeks.

Assays

Serum TNFα levels were measured from blood samples collected immediately before and after each infliximab or placebo infusion at weeks 0, 2, and 6, as well as at weeks 1, 10, 14, 20, and 28. Serum was separated and stored at −70°C until analyzed. TNFα was assayed using a validated assay kit (R&D Systems Human TNFα/ TNFSF2 QuantiGlo ELISA Kit).

IL-6 and CRP levels were measured from samples collected before and after the study agent infusion at week 0, before the study agent infusion at weeks 2 and 6, and at weeks 1, 10, 14, 20, and 28. IL-6 was assayed using the human IL-6 QuantGlo Immunoassay Kit (R&D Systems Laboratories) and CRP, using the validated high sensitivity CRP assay method (rate nephelometry) from Quest Laboratories (Quest Diagnostics).

Serum infliximab levels were measured from blood samples collected immediately before and after each infliximab or placebo infusion at weeks 0, 2, and 6, as well as at weeks 1, 10, 14, 20, and 28, with the use of an enzyme-linked immunoassay. The lowest level of infliximab that could be reliably detected using the assay was 0.06 μg/mL.
Statistical Analyses

Patients were included in the analysis according to the intention-to-treat principle, whether or not they received the study drug at specified time points. Applying last observation carried forward for missing data, analysis of the primary efficacy endpoint used an ordered alternative Cochran Mantel-Haenszel Test with scores of 1, 2, and 3 for worse, unchanged, and improved, respectively. For the analysis of major clinical events, the Kaplan-Meier method was used to describe the occurrence of events, and the log-rank test and proportional hazards regression analysis were used to test for treatment-group differences. Between-treatment comparisons of changes in left ventricular ejection fraction and Minnesota Living With Heart Failure scores were carried out by using a nonparametric test using van der Waerden scores.

This pilot study was powered to detect major differences between treatment groups. Assuming that the proportions of placebo patients would have been sufficient to detect rates in the combined infliximab groups (45%, 42%, and 13%, respectively), a sample size of 150 patients would have been sufficient to detect rates in the combined infliximab (45%, 42%, and 13%, respectively), a sample size of 150 patients with improved, unchanged, and worsened clinical status at week 14 would have been sufficient to detect rates in the placebo group and 16% in the 10 mg/kg infliximab group. The most common reason for permanent discontinuation of the study medication was an adverse event (6 patients). One patient who was randomized to 10 mg/kg infliximab received 5 mg/kg infliximab at each of the 3 infusion visits but was included in the 10 mg/kg group for efficacy analyses, according to the intention-to-treat principle.

Effect of Infliximab on Clinical Status

Changes in clinical status in the patients randomized to either dose of infliximab were not significantly different than in those randomized to placebo, either at 14 weeks (the primary endpoint) or at 28 weeks (the end of the prespecified period of follow-up) (Table 2). However, patients in the 10 mg/kg infliximab group were more likely than those in the other 2 groups to experience worsening of their clinical status at both 14 weeks (22% versus 8% in the placebo group and 10% in the 5 mg/kg infliximab group) and at 28 weeks (31% versus 14% in placebo group and 16% in the 5 mg/kg infliximab group) (Table 2).
Effect of Infliximab on Major Clinical Events
The increased risk of worsening clinical status in patients in the 10 mg/kg infliximab group was primarily related to an increased risk of major adverse clinical events in that group. Specifically, through 28 weeks, patients in the 10 mg/kg infliximab group were more likely to die or be hospitalized for heart failure than patients in the placebo group (hazard ratio 2.84, 95% confidence interval 1.01 to 7.97; nominal P = 0.043 using log-rank test) (Table 3 and Figure 1). Patients in the 10 mg/kg infliximab group were more likely to be hospitalized for heart failure or for any reason than patients in the placebo or 5 mg/kg infliximab groups (Table 3 and Figure 1).

Effect of Infliximab on Quality of Life
Median scores for the Minnesota Living With Heart Failure questionnaire at baseline were 52.0, 53.0, and 52.0 in the placebo, 5 mg/kg infliximab, and 10 mg/kg infliximab groups, respectively. There were no significant changes in quality of life scores among the 3 treatment groups either at 14 weeks (−4.0, −6.5, and −4.0 for placebo, 5 mg/kg, and 10 mg/kg [P = 0.829]) or at 28 weeks (0.0, −3.0, and −6.0 for placebo, 5 mg/kg, and 10 mg/kg, respectively [P = 0.811]).

Serum Levels of Infliximab and Effect on Surrogate Markers
Median serum levels of infliximab rose immediately with each infusion of the drug and, for at least 14 weeks, remained above levels that have been associated with clinical benefit in patients with rheumatoid arthritis (Figure 2).17

At baseline, median values for CPR were 6.2, 2.2, and 4.4 mg/L in the placebo, 5 mg/kg infliximab, and 10 mg/kg infliximab groups, respectively; values for IL-6 were 3.7, 3.2, and 3.8 pg/mL, respectively; and values for TNFα were 6.0, 5.7, and 6.6 pg/mL, respectively. Treatment with both doses of infliximab was associated with a reduction in serum levels of CRP and IL-6 within the first week; both markers remained below baseline for 14 weeks and gradually returned toward baseline levels by 28 weeks (Figure 3). Measured serum levels of TNFα in the infliximab groups were also reduced immediately after each infusion but were elevated above baseline values at all other time points through the 28-week period (Figure 4). An in vitro bioactivity assay based on the WEHI cell viability method demonstrated an apparent lack of free biologically active TNFα in samples that had increased levels of immunodetectable TNFα.

Changes in inflammatory markers were accompanied by changes in the left ventricular ejection fraction. At 14 weeks (when levels of CRP and IL-6 were suppressed), left ventricular ejection fraction increased in patients treated with infliximab (mean changes from baseline of 3.5% with 5 mg/kg infliximab, 2.1% with 10 mg/kg infliximab, and 0.8% with placebo, P = 0.039 for placebo versus both infliximab groups.

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TABLE 3. Major Clinical Events During the Study

<table>
<thead>
<tr>
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<th>Placebo (n=49)</th>
<th>Infliximab 5 mg/kg (n=50)</th>
<th>Infliximab 0 mg/kg (n=51)</th>
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<tr>
<td>Hospitalization for</td>
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<td>heart failure</td>
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<td>0 to 28 weeks</td>
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<td>20</td>
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<td>Death (any cause)</td>
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<td>3</td>
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<tr>
<td>0 to 1 year</td>
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<td>8</td>
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Values are No. of patients experiencing major clinical events, by time period and treatment group.
combined). However, by 28 weeks (when levels of CRP and IL-6 had increased toward baseline), changes in left ventricular ejection fraction in the infliximab groups were no longer significantly different than in the placebo group (mean increases from baseline of 4.2%, 1.3%, and 3.4% in the 5 mg/kg infliximab, 10 mg/kg infliximab, and placebo groups, respectively).

**Adverse Events**

A similar proportion of patients in each of the 3 treatment groups reported 1 or more adverse events during the first 28 weeks of the study (Table 4). Dizziness, dyspnea, hypotension, and angina were reported more frequently in infliximab-treated patients. Serious adverse events were reported more frequently in the 10 mg/kg infliximab group than in the other 2 groups (44.0% versus 29.2% in the placebo group and 23.5% in the 5 mg/kg group), a finding that was primarily related to the higher frequency of reports of heart failure in that group (22.0% with 10 mg/kg versus 8.3% with placebo and 2.0% with 5 mg/kg). Other serious adverse events reported in greater than 2% of the combined infliximab groups included dyspnea (4.2%, 5.9%, and 6.9% in the placebo, 5 mg/kg, and 10 mg/kg groups, respectively); chest pain (0.0%, 2.0%, and 6.0%); and pneumonia (2.1%, 3.9%, and 2.0%). Serious infections occurred in 2.1%, 5.9%, and 8.0% of the placebo, 5 mg/kg, and 10 mg/kg infliximab groups.

Of 96 infliximab-treated patients with serum samples evaluable for antibodies to infliximab, 16 (16.7%) had detectable antibodies, and titers were $\geq 1:20$ in 15 of these patients.

**Discussion**

Although the current study was designed as a pilot experience, the observations carried out during the course of this trial do not support the utility of TNFα antagonism with infliximab as a treatment for chronic heart failure in the doses utilized in this study. Patients treated with infliximab (at 5 mg/kg or at 10 mg/kg per infusion) did not show an improvement in any of a broad range of objective and subjective clinical assessments. Furthermore, treatment of patients with moderate-to-severe chronic heart failure with high doses of infliximab (10 mg/kg per infusion) was associated with worsening clinical status, an increased likelihood of hospitalization, and a high frequency of worsening heart failure reported as a serious adverse event. The increased risk of adverse clinical events associated with the use of high doses of infliximab was not only observed during treatment but also persisted for up to 5 months after the cessation of therapy.

Infliximab failed to produce clinical benefits in this study, even though the drug exerted its expected biological effects. Serum levels of CRP and IL-6 were suppressed in both infliximab groups relative to placebo for at least 14 weeks.
The lack of benefit may have been related to the short duration of effective treatment (~14 weeks); this may have been particularly true for a drug that is believed to exert any benefit by altering fundamental processes that affect cardiac structure and function. However, previous trials have shown that improvements in physiological variables are not reliably translated into measurable clinical benefits, even when the treatment is sustained for long periods.18,19

The results of the current trial differ substantially from those reported with the use of TNFα antagonists in experimental models of heart failure. Administration of the soluble TNFα receptor etanercept attenuates adverse cardiac effects associated with the infusion of TNFα in rats.20 The administration of both a soluble tumor necrosis factor encoding adenovirus and a monoclonal anti-TNFα antibody similar to infliximab but biologically active in mice is associated with beneficial cardiac effects in genetically altered mice with heart failure secondary to overexpression of TNFα.21,22 and suppression of TNFα exerts favorable effects in rats with heart failure produced by coronary artery ligation.23 Unfortunately, favorable results with therapeutic agents in experimental models of heart failure have frequently not been replicated in controlled clinical trials.24,25

Despite the encouraging results of the small pilot trial with etanercept, the results of 2 large-scale, multicenter trials of this TNFα antagonist in 2048 patients with moderate-to-severe heart failure did not demonstrate any clinical benefits associated with the use of etanercept and suggested that etanercept might adversely affect the courses of patients with chronic heart failure in a dose-dependent manner.26 The results of these definitive trials are consistent with the observations of the current study.

What might explain the tendency for TNFα antagonism to adversely affect the clinical course of patients with heart failure in a dose-dependent manner? Some reports have suggested that treatment with available TNFα antagonists might potentiate (rather than interfere with) the cardiac toxicity of TNFα. By complexing with circulating TNFα and thereby retaining it within the circulation, etanercept may prolong exposure of cardiac tissue to TNFα27 and potentially lead to cardiac toxicity. Similarly, when exposed to cells expressing transmembrane TNFα, infliximab can cause cell lysis in the presence of complement,28 an effect that would be undesirable if it occurred in cardiomyocytes in patients with heart failure. The toxicity of TNFα might be also enhanced if treatment with infliximab caused circulating levels of TNFα (which are immediately suppressed after administration of the drug) to rebound to levels substantially higher than those seen before the start of treatment (Figure 4). However, there is no direct evidence to suggest that any of these proposed mechanisms are operative in patients with heart failure. Biologically active TNFα could not be detected in serum samples with elevated levels of immunoreactive TNFα, suggesting that the QuantiGlo assay used for the measurement of serum TNFα detected not only free TNFα but also partially saturated TNFα–infliximab complexes, which are immunoreactive but biologically inactive.

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![Figure 4. Median serum concentrations of immunoreactive TNFα by treatment group. Serum TNFα levels were measured from blood samples collected at each study visit. At weeks 0, 2, and 6, serum TNFα was measured both before and after study agent infusions. Biologically active TNFα could not be detected in serum samples with elevated levels of immunoreactive TNFα, suggesting that the QuantiGlo assay used for the measurement of serum TNFα detected not only free TNFα but also partially saturated TNFα–infliximab complexes, which are immunoreactive but biologically inactive.](image-url)
of infliximab, are undetectable. A similar pattern of serum TNFα concentrations is seen in patients with Crohn’s disease who show sustained clinical benefits with infliximab.29

If treatment with TNFα antagonists does not potentiate the toxicity of TNFα, then what can explain the worsening of heart failure seen in studies with infliximab and etanercept? It has generally been assumed that the activation of cytokines plays a deleterious role in heart failure,30 but it is conceivable that increases in TNFα play an adaptive role—similar to that hypothesized for natriuretic peptides. By enhancing the production of vasoconstrictor nitric oxide, TNFα may play an important role in enhancing the production of adrenomedullin and other endogenous vasodilators and maintaining peripheral blood flow in patients with heart failure.31–33 Furthermore, TNFα may prevent apoptosis in myocytes under stress,34 and by enhancing the production of myocardial nitric oxide, the cytokine may attenuate responsiveness to β-adrenergic stimulation and thereby attenuate the toxicity associated with prolonged activation of the sympathetic nervous system.33,35–38

The existence of mechanisms by which cytokine activation may be beneficial (when taken together with the results of clinical trials with TNFα antagonists) challenge the conventional wisdom that TNFα acts as a deleterious factor in patients with chronic heart failure.

In conclusion, therapy with infliximab over a 6-week period did not produce clinical improvement in patients with moderate-to-severe heart failure followed for 14 to 28 weeks, and treatment with high doses (10 mg/kg) was associated with an increased risk of worsening heart failure. Although a similar risk was not observed with the 5 mg/kg doses of infliximab in the current study, an adverse effect at this lower dose (particularly during longer-term treatment) cannot be excluded. These findings raise unresolved questions about the role of TNFα in heart failure and important concerns about the safety of using TNFα antagonists (especially at high doses) for the treatment of noncardiac disorders in patients who also have moderate-to-severe heart failure. Whether infliximab can be used safely in patients with asymptomatic left ventricular dysfunction or mild symptoms of heart failure (NYHA class I/II) remains to be determined.

Appendix

Investigators and Study Centers (in Descending Order of Number of Patients Enrolled)

Dean Kereakes and Linda Martin, The Lindner Clinical Trial Center, Cincinnati, Ohio; Jerome L. Anderson and Carolyn Cater-Emmett, Cardiovascular Clinic, Oklahoma City, Okla; Ron Oren and Todd Jayden, University of Iowa, Iowa City, Iowa; Richard Gilmore and Myra Thomas, St Patrick Hospital, Lake Charles, La; Brian Jaski and Sue Harte, San Diego Cardiac Center, San Diego, Calif; Krishnaswami Vijayaraghavan and Debra Rothenbuehler, Arizona Heart Institute, Phoenix, Ariz; Martin R. Berk and Mary Ann Miller, Western PA Hospital, Pittsburgh, Pa; Irmina Gradus-Pizlo (CORE [Collaborative Organization for Research Endavors] investigator) and Mary Rawlings, Saint Louis University, St Louis, Mo; Leah Foster, Diane Licursi, Kim Hung Lo, Jennifer Toomey.

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References


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