Safety and Efficacy of a Soluble P75 Tumor Necrosis Factor Receptor (Enbrel, Etanercept) in Patients With Advanced Heart Failure

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Background—Although previous studies suggested that TNF may contribute to heart failure progression, it is unclear whether antagonizing TNF is beneficial in heart failure patients.

Methods and Results—Eighteen NYHA class III heart failure patients were randomized into a double-blind dose-escalation study to examine the safety and potential efficacy of etanercept, a specific TNF antagonist (Enbrel). Patients received placebo (6 patients) or an escalating dose (1, 4, or 10 mg/m²) of etanercept (12 patients) given as a single intravenous infusion. Safety parameters and patient functional status were assessed at baseline and at days 1, 2, 7, and 14. There were no significant side effects or clinically significant changes in laboratory indices. There was, however, a decrease in TNF bioactivity and a significant overall increase in quality-of-life scores, 6-minute walk distance, and ejection fraction in the cohort that received 4 or 10 mg/m² of etanercept; there was no significant change in these parameters in the placebo group.

Conclusions—A single intravenous infusion of etanercept was safe and well tolerated in patients with NYHA class III heart failure. These studies provide provisional evidence that suggests that etanercept is sufficient to lower levels of biologically active TNF and may lead to improvement in the functional status of patients with heart failure. (Circulation. 1999;99:3224-3226.)

Key Words: tumor necrosis factor ▪ heart failure ▪ etanercept

Since the original report of elevated levels of tumor necrosis factor (TNF) in patients with heart failure, there has been increasing speculation that TNF may contribute to the progression of heart failure by virtue of the direct toxic effects that this cytokine exerts on the heart and the circulation. For example, experimental studies have shown that pathophysiologically relevant peripheral and/or elevated intramyocardial levels of TNF are sufficient to mimic many aspects of the heart failure phenotype, including left ventricular (LV) dilatation, LV dysfunction, and activation of fetal gene programs. Moreover, TNF can produce LV dysfunction, pulmonary edema, and cardiomyopathy in human subjects.

Recent experimental studies from this laboratory have shown that a soluble p75 TNF receptor fusion protein (etanercept) that binds to TNF and functionally inactivates this cytokine is sufficient to reverse some of the deleterious cardiovascular effects of TNF in vitro and in vivo. To extend these early preclinical studies, we examined the safety and efficacy of etanercept in patients with advanced heart failure.

See p 3213

Methods

Study Population

We studied 18 NYHA class III heart failure patients who had an initial screening ejection fraction <35% and elevated circulating plasma levels of TNF >3.0 pg/mL (>2 SD above the mean TNF level for normal subjects). The protocol was approved by the Baylor College of Medicine Institutional Review Board.

Study Protocol and Objectives

The study was a randomized, double-blind, placebo-controlled, dose-escalation trial. The primary objectives were to evaluate the safety of etanercept in patients with NYHA class III heart failure and to assess clinical and laboratory indices for preliminary evidence of improvement in LV ejection fraction, patient functional status, and TNF bioactivity. The secondary objective was to evaluate the systemic pharmacokinetics of a single intravenous dose of etanercept. For safety purposes, the study was designed as a dose-escalation study consisting of 3 patient cohorts. Each cohort consisted of 6 patients, 2 of whom received placebo and 4 of whom received etanercept. The order of drug delivery was random within each cohort, such that the patient and investigators were blinded at the time of study drug administration. The first group received 1 mg/m², which was intended to serve as a no-dose effect, whereas the second and third groups received 4 and 10 mg/m² of etanercept, respectively, which were anticipated to have biological effects.

The baseline evaluation consisted of a history and cardiopulmonary examination, a 2D echocardiogram for measurement of ejection fraction, routine laboratory tests, and patient functional status. Etanercept or placebo (diluent) was administered as a single intravenous infusion over 30 minutes. Repeated evaluations of blood pressure, heart rate, and clinical status were performed for the first 6
hours after administration of study drug to observe for side effects. All other data were obtained at baseline and on days 1, 2, 7, and 14.

Safety of Etanercept
Patients were evaluated for adverse events for 14 days, including a serial assessment of heart rate and blood pressure, hemoglobin/hematocrit, white blood cell count, platelet count, serum electrolytes, and serum creatinine. Testing for antibodies to etanercept was performed at baseline and on day 14, as described.4

Systemic Levels and Biological Effects of Etanercept
To obtain an indirect assessment of the pharmacokinetics of a single dose of etanercept, we measured circulating levels of the soluble type 2 (p75) TNF receptor (sTNFR2) by ELISA (R&D Systems) at baseline, at 6 hours, and on days 1, 2, 7, and 14. Etanercept contains 2 molecules of the extracellular portion of sTNFR2 linked to the Fc portion of the IgG1 molecule. Hence, changes in circulating levels of sTNFR2 by ELISA should largely reflect the presence of etanercept in the circulation. To assess the effects of etanercept on TNF bioactivity, we used an L929 assay.2 Changes in the circulating plasma levels of interleukin-6 (IL-6) were determined by ELISA (R&D Systems).4

Functional Effects of Etanercept
To assess the functional effects of etanercept, we assessed changes in the quality of life using a visual analogue scale, the distance traveled during a 6-minute uncoached walk test, and the LV ejection fraction, which was determined by echocardiography using a modified Simpson’s rule to calculate LV volumes. All echocardiographic analyses were performed by 1 experienced observer. Changes in quality of life were measured by the visual analogue scale in which the patient assesses his or her overall feeling of well-being on an ordinal scale ranging from 0 to 100, with 100 as the best possible score.

Statistical Analysis
Data are expressed as mean±SEM. A Student’s t test or Fisher’s exact test was used to test for differences in baseline characteristics. A factorial repeated-measures ANOVA was used to assess changes between each of the 4 groups (placebo and 1, 4, and 10 mg/m² etanercept). A 1-way repeated-measures ANOVA was used to assess changes in quality of life, 6-minute walk distance, ejection fraction, TNF bioactivity, and safety parameters within individual groups; post hoc ANOVA testing was performed when appropriate. Factorial repeated-measures ANOVA was also used to assess changes in safety parameters between the placebo and etanercept groups.

Results
Patient Demographics
Table 1 shows the baseline characteristics of the patients who received placebo and the 12 patients who received etanercept. There was no significant difference in age, cause of heart failure, ejection fraction, or peripheral TNF levels between groups. All of the patients received ACE inhibitors, 94.4% received digoxin, 11% received β-blockers, and 11% received amlodipine; there was no significant difference between groups with respect to medication use.

Safety of Etanercept
None of the patients developed side effects after the infusion of etanercept, nor were there any significant differences in heart rate, blood pressure, or hematological and serum chemical parameters between the placebo and etanercept groups (data not shown). No antibodies to etanercept were detected.

| TABLE 1. Baseline Clinical Characteristics |
|----------------|----------------|
|                | Placebo (n=6) | Etanercept (n=12) | P     |
| Age, y         | 63.3±3.9      | 63.3±3.0          | 1.0   |
| Sex, M/F       | 5/1           | 12/0              | 0.33  |
| Cause, IHD/DCM | 4/2           | 11/1              | 0.25  |
| EF, %          | 23.3±3.0      | 29.6±3.1          | 0.22  |
| TNF, pg/mL     | 7.0±1.1       | 6.1±0.6           | 0.46  |
| QOL            | 65±7.1        | 55.6±5.5          | 0.32  |
| Walk distance, m | 249.9±51.0    | 228.9±21.1        | 0.66  |

IHD indicates ischemic heart disease; DCM, dilated cardiomyopathy; EF, ejection fraction; QOL, quality of life score; and walk distance, 6-minute walk distance.

Peripheral Levels and Biological Effects of Etanercept
Figure 1B shows the changes in the plasma levels of sTNFR2 (which should predominantly reflect changes in the circulating level of etanercept) in the patients who received etanercept. The peripheral levels were highest at 6 hours after administration and then declined thereafter (P<0.001 by ANOVA), but they were still elevated at day 7 compared with baseline values (P<0.05). There was no significant change in the level of sTNFR2 in the patients who received etanercept (P=0.04 by ANOVA); moreover, these levels remained significantly depressed at day 14 (P<0.05). Figure 1C shows that there was a small but significant decrease in IL-6 levels in the etanercept group (P=0.003 by ANOVA).

Functional Effects of Etanercept
Table 2 shows the values for quality of life, 6-minute walk distance, and ejection fraction at baseline and on days 1, 2, 7, and 14 for patients who received placebo and the entire cohort of patients who received etanercept. When analyzed by a factorial repeated-measures ANOVA, there was no significant difference in these parameters between the 4 groups of patients who received either placebo or 1, 4, or 10 mg/m² of etanercept except for ejection fraction, for which the difference was of borderline significance (P=0.04). Because of the relatively small sample size (n=4 for each dose of etanercept), we next tested for differences within individual groups. Although there were no significant changes from baseline in any parameter for the placebo group, there was a significant improvement in the quality-of-life score in the patients who received etanercept (P=0.003) and a small but statistically significant increase in the ejection fraction (P<0.01). There was, however, no significant change in the 6-minute walk distance in the etanercept group. Because the 1-mg/m² dose was included in the study design as a “no-dose” effect, we also repeated the above analyses after excluding the 4 patients who received 1 mg/m². As shown in Figure 1D, 1E, and 1F, respectively, there was a significant overall improvement in the quality-of-life score (P=0.001), 6-minute walk distance (P=0.01), and ejection fraction (P=0.03) for the patients who received 4 or 10 mg/m² of etanercept.
Discussion

Although previous preclinical studies have supported a role for TNF in the pathogenesis of heart failure,\(^2,3\) the clinical experience with TNF antagonism in heart failure patients is limited. The results of this study, as well as a previous study with pentoxifylline in patients with dilated cardiomyopathy,\(^6\) support the concept that TNF is a potentially important therapeutic target in heart failure patients. In this study, we show that a single intravenous infusion of etanercept was safe and well tolerated in patients with NYHA class III heart failure. Moreover, a single intravenous infusion of etanercept was sufficient to lower levels of biologically active TNF (Figure 1A) and lead to improvements in the functional status of patients (Figure 1D and 1E). Although the results of this phase 1 study must be regarded as provisional because of the relatively small numbers of patients and the relatively short duration of follow-up, this study does show that etanercept can be given safely to heart failure patients. Whether the effects that were observed with etanercept in the present study can be sustained when etanercept is given repeatedly over longer periods of time and in larger patient populations will be addressed in the planned multicenter Randomized Etanercept North American Strategy to Study Antagonism of CytokinEs (RENAISSANCE).

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