Clinical Investigation and Reports

Targeted Anticytokine Therapy in Patients With Chronic Heart Failure

Results of the Randomized Etanercept Worldwide Evaluation (RENEWAL)

Douglas L. Mann, MD; John J.V. McMurray, MD, FRCP, FESC; Milton Packer, MD; Karl Swedberg, MD, PhD, FESC; Jeffrey S. Borer, MD; Wilson S. Colucci, MD; Jacques Djian, MD, FESC; Helmut Drexler, MD; Arthur Feldman, MD, PhD; Lars Kober, MD; Henry Krum, MD, PhD, FRACP; Peter Liu, MD; Markku Nieminen, MD, PhD; Luigi Tavazzi, MD; Dirk Jan van Veldhuisen, MD, PhD; Anders Waldenstrom, MD, PhD; Marshelle Warren, MD; Arne Westheim, MD; Faiez Zannad, MD, PhD; Thomas Fleming, PhD

Background—Studies in experimental models and preliminary clinical experience suggested a possible therapeutic role for the soluble tumor necrosis factor antagonist etanercept in heart failure.

Methods and Results—Patients with New York Heart Association class II to IV chronic heart failure and a left ventricular ejection fraction ≤0.30 were enrolled in 2 clinical trials that differed only in the doses of etanercept used. In RECOVER, patients received placebo (n=373) or subcutaneous etanercept in doses of 25 mg every week (n=375) or 25 mg twice per week (n=375). In RENAISSANCE, patients received placebo (n=309), etanercept 25 mg twice per week (n=308), or etanercept 25 mg 3 times per week (n=308). The primary end point of each individual trial was clinical status at 24 weeks. Analysis of the effect of the 2 higher doses of etanercept on the combined outcome of death or hospitalization due to chronic heart failure from the 2 studies was also planned (RENEWAL). On the basis of prespecified stopping rules, both trials were terminated prematurely owing to lack of benefit. Etanercept had no effect on clinical status in RENAISSANCE (P=0.17) or RECOVER (P=0.34) and had no effect on the death or chronic heart failure hospitalization end point in RENAISSANCE (etanercept to placebo relative risk=1.1, 95% CI 0.91 to 1.33, P=0.33).

Conclusions—The results of RENEWAL rule out a clinically relevant benefit of etanercept on the rate of death or hospitalization due to chronic heart failure. (Circulation. 2004;109:1594-1602.)

Key Words: heart failure ▪ tumor necrosis factor ▪ etanercept ▪ cytokines
cell surface membranes. Thus far, treatment with etanercept has resulted in clinical improvements in patients with rheumatoid arthritis, ankylosing spondylitis, and psoriasis.\textsuperscript{6–8} Preclinical studies showed that etanercept reversed some of the deleterious effects of TNF in vitro and in vivo.\textsuperscript{3,9} Moreover, phase I safety studies showed that a single intravenous infusion of etanercept was safe and well tolerated and led to an improvement in the functional status of heart failure patients.\textsuperscript{10} In a subsequent study, biweekly injections of etanercept for 3 months resulted in a significant increase in left ventricular ejection fraction and a significant decrease in left ventricular volumes.\textsuperscript{11} On the basis of the preclinical and clinical studies, 2 multicenter clinical trials were designed to test the effect of etanercept on patient functional status and morbidity/mortality.

\section*{Methods}

\subsection*{Study Design}

Two similar double-blind, randomized, placebo-controlled multicenter clinical trials were conducted, 1 in Europe, Israel, Australia, and New Zealand, known as Research into Etanercept Cytokine antagonism in VEntricuLaR dysfunction (RECOVER), and the other in North America, known as Randomized Etanercept North American Strategy to Study AntagoNism of CytokinEs (RENAISSANCE). The trials differed, importantly, only in the doses of etanercept used. In RECOVER, the patients were randomized on a 1:1:1 basis to placebo or etanercept 25 mg SC once weekly (QW) or twice weekly (BIW), whereas in RENAISSANCE, patients were randomized to placebo or etanercept 25 mg BIW or 25 mg 3 times weekly (TIW).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
& \multicolumn{3}{c|}{RECOVER} & \multicolumn{3}{c|}{RENAISSANCE} \\
& Placebo & Etanercept 25 mg QW & Etanercept 25 mg BIW & Placebo & Etanercept 25 mg BIW & Etanercept 25 mg TIW \\
\hline
Mean (SD) age, y & 64.6 (10.8) & 64.8 (10.3) & 64.1 (10.4) & 62.6 (11.9) & 61.8 (12.1) & 62.4 (11.0) \\
Mean (SD) LVEF & 24 (5) & 24 (5) & 24 (5) & 22 (6) & 22 (5) & 22 (6) \\
Mean (SD) SBP, mm Hg & 122 (18) & 122 (18) & 122 (18) & 110 (16) & 110 (17) & 108 (16) \\
Mean (SD) DBP, mm Hg & 74 (12) & 74 (12) & 74 (12) & 74 (12) & 74 (11) & 74 (11) \\
Mean (SD) heart rate, bpm & 99 & 99 & 99 & 82 & 85 & 83 \\
White & <1 & <1 & <1 & 18 & 15 & 17 \\
Nonwhite & 75 & 77 & 81 & 77 & 77 & 81 \\
Male & 60 & 62 & 61 & 60 & 63 & 62 \\
Ischemic etiology & 28 & 27 & 27 & 23 & 23 & 24 \\
NYHA class & 43 & 45 & 45 & 47 & 47 & 47 \\
IV & 25 & 25 & 24 & 26 & 25 & 24 \\
Comorbidity & 3 & 3 & 3 & 4 & 5 & 5 \\
Hypertension & 46 & 45 & 43 & 49 & 60 & 56 \\
Diabetes mellitus & 36 & 34 & 36 & 34 & 41 & 37 \\
Medical treatment & 53 & 56 & 53 & 52 & 81 & 83 \\
Digoxin/digitalis & 85 & 83 & 87 & 82 & 77 & 79 \\
ACE inhibitor & 13 & 14 & 12 & 16 & 23 & 19 \\
ARB & 64 & 62 & 62 & 63 & 59 & 59 \\
β-Blocker & 37 & 44 & 44 & 34 & 37 & 32 \\
K-sparing diuretic & 99 & 99 & 99 & 99 & 98 & 100 \\
Any diuretic & \\
\hline
LVEF indicates left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; and ARB, angiotensin-receptor blocker.
\end{tabular}
\caption{Baseline Demographics and Characteristics for RECOVER and RENAISSANCE}
\end{table}
The intent was for each trial to enroll 900 patients (Figure 1). The primary end point in RENAISSANCE and RECOVER was a change in clinical status from baseline to 24 weeks. This end point is based on a composite score, wherein patients are considered improved, worsened, or unchanged on the basis of death, CHF hospitalization, New York Heart Association (NYHA) class, and patient global assessment, as detailed previously.12

A prespecified analysis of the effect of etanercept on longer-term morbidity/mortality was also planned. This analysis, which was referred to as the Randomized EtaNErcept Worldwide evALuation (RENEWAL), combined the BIW treatment arm of RECOVER with the BIW and TIW arms of RENAISSANCE and compared these with the pooled placebo arms from both studies, with an anticipated total of 1500 patients. The primary end point of RENEWAL was the composite of death (of all causes) or hospitalization for or with CHF. The RENEWAL analysis was event driven (see statistical analysis). Secondary end points included all-cause mortality and the total number of hospitalizations and emergency room visits for or with worsening CHF, as well as, at 24 weeks, change in NYHA class, patient global assessment, and quality of life.

Patients

The main inclusion criteria were age 18 to 85 years; NYHA class II to IV; ischemic or nonischemic etiology; left ventricular ejection fraction ≥0.30; stable doses of diuretic, ACE inhibitor (unless not tolerated), and β-blocker and/or spironolactone (if taking) for ≥3 months; and 6-minute walk distance of <375 m (or <425 m if hospitalized for CHF within previous 6 months). The main exclusion criteria were severe infection within 1 month, surgically correctable causes of heart failure, other serious illness, acute myocardial infarction or hospitalization (3 months), and recent (3 months) or planned surgery/coronary revascularization. The studies received ethics approval in all participating centers, and all patients gave written informed consent.

Statistical Analyses

In RECOVER and RENAISSANCE, the clinical composite score was analyzed with a Cochran-Mantel-Haenszel test. The statistical assumptions in RECOVER were that in the placebo group, 40% of the patients would be worse, 42% would remain unchanged, and 18% would be improved, and in the treatment group (QW and BIW etanercept), 28% of the patients would be worse, 42% would remain unchanged, and 30% would be improved. There was 90% power for the primary hypothesis test of 25 mg BIW versus placebo and 81% power for the conditional primary hypothesis test of 25 mg QW versus placebo, both tested at the 2-sided 0.04 level. The statistical assumptions in RENAISSANCE were that in the placebo group, 25% of the patients would be worse, 55% would remain unchanged, and 20% would be improved, and in the treatment group (BIW and TIW etanercept), 17% of the patients would be worse, 53% would remain unchanged, and 30% would be improved. There was 84% power for each comparison of an etanercept treatment arm to placebo when controlling the overall type I error rate at 0.04. In the RENEWAL trial, using a stratified log-rank analysis, 389 events would provide 90% power for a 2-sided 0.01 level test to detect a 32.4% relative reduction in risk for this end point, when the combined BIW and TIW etanercept treatment arms were compared with placebo. To control the overall type I error rate within each study at 0.05, analyses of the clinical status composite were conducted at the 2-sided 0.04 level, and the combined analysis of all-cause mortality or CHF hospitalization was conducted at the 2-sided 0.01 level. The log-rank statistic for the RENEWAL analysis was stratified by study, baseline β-blocker status, and NYHA functional class.

Safety Monitoring and Stopping Guidelines

A single independent Data Monitoring Committee (DMC) monitored both RENAISSANCE and RECOVER. The DMC could recommend modifications to the protocols to enhance patient safety or quality of trial conduct. Early termination of the studies could be recommended if there was strong evidence that etanercept would show no benefit at the end of the study for the clinical composite end point. Such evidence was defined as having sufficiently unfavorable interim results in the 4 pairwise comparisons with placebo (by comparison of

Figure 2. Analysis of clinical status composite score for RECOVER and RENAISSANCE trials in placebo and etanercept groups (number of patients who had completed planned 24-week treatment when these trials were stopped).

Figure 3. Kaplan-Meier analysis of time to death or heart failure hospitalizations in placebo and etanercept group (BIW and TIW) in RENEWAL analysis.
each of the 2 dose groups with placebo in both RECOVER and RENAISSANCE) that the conditional probability for achieving a positive effect on the clinical composite end point (if one continued to assume the protocol-specified targeted level of benefit) was 0.25 for each of these 4 pairwise comparisons. Early termination could also be recommended by the DMC for conclusive interim results on the morbidity/mortality end point in RENEWAL, either because interim data for the combined end point of mortality and hospitalization for heart failure would be sufficiently unfavorable as to rule out a 10% reduction in relative risk or because interim data for all-cause mortality would be sufficiently favorable as to establish benefit, where both of these assessments would be guided by use of the O’Brien-Fleming monitoring boundary.

Results

Patients Enrolled

Between June 1999 and December 2000, a total of 1123 patients from 194 centers were enrolled in RECOVER. In RENAISSANCE, 925 patients from 105 centers were randomized between March 1999 and January 2001. The baseline characteristics of the patients are summarized in Table 1. The placebo and etanercept groups in each study were generally well matched, although there were imbalances between treatment groups for diabetes in both studies. There was also an imbalance in the number of patients with a history of diabetes.

Table 2 shows the main outcomes in RECOVER, RENAISSANCE, and RENEWAL. The results for the primary endpoint of death or CHF hospitalization are presented for each study. The relative risk (RR) and 95% confidence intervals (CI) for active vs placebo group are provided. The P-values for Cox regression analysis are also given. The model includes terms for the study, NYHA functional classification, and baseline use of β-blockers. P values for the Cox regression, etc, are already written plus key.

Figure 4. Kaplan-Meier analysis of time to death in placebo and etanercept group (BIW and TIW) in RENEWAL analysis.
of hypertension, which was lower in the group in RENAISSANCE.

Early Termination of Studies
On March 22, 2001, the DMC recommended termination of both studies because the prespecified criteria for stopping due to lack of benefit were met in the RECOVER and RENAISSANCE studies and the RENEWAL analysis. The median time from randomization to the last visit was 5.7 months in RECOVER and 12.9 months in RENAISSANCE. At the time the studies were closed, 37% and 73% of the patients in RECOVER and RENAISSANCE, respectively, had completed the 24-week evaluation. One percent or less of any treatment group of RECOVER or RENAISSANCE was lost to follow-up for assessment of vital status, and 0.4% and 0.9% of patients withdrew consent for evaluation of clinical status in RECOVER and RENAISSANCE, respectively.

Primary End Point in RENAISSANCE and RECOVER
Figure 2 shows that there were not significant differences between placebo and etanercept with respect to change in the clinical composite score from baseline to 24 weeks (or the last evaluated visit before study stoppage) in either RECOVER ($P=0.34$ overall; $P=0.76$ QW; $P=0.27$ BIW) or RENAISSANCE ($P=0.17$ overall; $P=0.07$ BIW; $P=0.17$ TIW). In RENAISSANCE, there was a higher proportion (29%, $P=0.046$) of patients given etanercept 25 mg BIW than placebo patients (20%) in the "worsened" category at 24 weeks; however, this difference was not observed in RECOVER.

Outcome of Death or CHF Hospitalization in RENAISSANCE
For the death and CHF hospitalization end point, the log-rank analysis was stratified by trial, baseline NYHA class, and β-blocker use and included 682 placebo patients (309 from RENAISSANCE and 373 from RECOVER) and the 991 etanercept patients (375 BIW patients from RECOVER and 308 BIW and 308 TIW patients from RENAISSANCE). In RENAISSANCE, there were 100 events in 309 patients in the placebo group and 226 events in 616 patients in the combined etanercept groups; in RECOVER, there were 66 events in 373 patients in the placebo group and 60 events in 375 patients in the BIW etanercept group. These data yielded an estimated etanercept-to-placebo relative risk of 1.1 (95% CI 0.91 to 1.33; $P=0.33$; Figure 3). Hence, the results were sufficiently unfavorable as to exclude a 10% reduction in the rate of death or CHF hospitalization with etanercept.

Secondary Outcomes in RENEWAL
With regard to overall mortality, in RENAISSANCE, there were 44 deaths in 309 patients in the placebo group and 116 deaths in 616 patients in the combined etanercept groups; in RECOVER, there were 33 deaths in 373 patients in the placebo group and 27 deaths in 375 patients in the BIW etanercept group. These data yielded an estimated etanercept-to-placebo relative risk of 1.13 (95% CI 0.86 to 1.50; $P=0.39$; Figure 4). There were no significant differences in any of the other secondary outcomes.

RENEWAL Subgroup Analyses
Figure 5 summarizes the RENEWAL subgroup analyses. Overall, there were no significant differences between treatments for any of the subgroups.

Adverse Events and Safety
Table 3 summarizes the incidence of adverse events that occurred in both trials. Adverse events that occurred in more than 10% of patients overall in the RENAISSANCE trial were upper respiratory tract infections, dizziness, injection-site reaction, pain, diarrhea, chest pain, bronchitis, headache, flu syndrome, constipation, and cough. Of these events, injection-site reaction, bronchitis, and constipation occurred statistically significantly ($P<0.05$) more frequently in patients receiving etanercept than in those given placebo. In the RECOVER trial, adverse events that occurred in more than 5% of patients were upper respiratory infection, injection-site reaction, bronchitis, dizziness, pneumonia, chest pain, abdominal pain, angina pectoris, flu syndrome, increased cough, and dyspnea; there were no statistically significant differences ($P>0.10$) among the 3 treatment groups for these events.

Table 4 summarizes the incidence of serious and nonserious infections in both trials and shows a trend ($P=0.067$) toward more infections, overall, in the etanercept-treated
though the reasons for this lack of benefit of etanercept are not known, there are several possible explanations. One possibility is that proinflammatory cytokines do not play a deleterious role in the pathophysiology of CHF. A second possibility is that the doses of etanercept that we used were not sufficient to neutralize circulating and/or myocardial tissue levels of TNF. A third possibility is that the targeted approach that was taken was not sufficient to disrupt the network of inflammatory mediators (eg, interleukin-1β, interleukin-6, and nitric oxide) that are activated in heart failure.13 Targeted anticytokine treatment with etanercept has been beneficial in some (eg, rheumatoid arthritis, ankylosing spondylitis, and psoriasis6–8) but not all (eg, Crohn’s disease and systemic sepsis14,15) conditions in which TNF is thought to play an important pathophysiological role. It is not possible to definitively address these latter 2 possibilities because neither circulating levels of inflammatory mediators nor measures of TNF bioactivity were analyzed systematically in RECOVER and RENAISSANCE. A fourth possibility is that the short-term benefits of etanercept observed in the earlier small phase I studies in CHF were offset in the long term by the ability of etanercept to stabilize biologically active (homotrimeric) TNF, thereby acting as an TNF agonist.16 The observation that there was a higher proportion of patients in the worsened category in RENAISSANCE, in which patients were exposed to etanercept for the longest time, is consistent with this point of view. A final consideration suggested by experimental studies is that physiological levels of TNF are necessary for cardiovascular homeostasis.17,18 Accordingly, sustained lowering of TNF may have contributed to the higher proportion of patients in the worsened category because of loss of the beneficial aspects of cytokine signaling.

The results of the present study need to be discussed in light of the recently reported ATTACH (Anti-TNF-α in Congestive Heart Failure) trial,19 a smaller study of 150 patients that used a chimeric anti-TNF antibody that exerts anti-inflammatory effects by binding to and neutralizing circulating TNF, as well as lysing TNF-expressing cells through complement fixation. In ATTACH, there was a significant increase in death and heart failure hospitalization at 28 weeks in the patients who received infliximab 10 mg/kg. Although we cannot discount the possibility that the worsening heart failure observed in the ATTACH trial and the suggestion of worsening heart failure outcome seen in the RENAISSANCE trial both may have been related to excessive TNF antagonism or loss of the beneficial aspects of cytokine signaling, there are other possible explanations, including “TNF rebound”20 and complement fixation, that may have contributed to worsening heart failure outcomes in the ATTACH trial. However, precise mechanistic explanations for the differences in outcomes in the ATTACH and RENEWAL trials are not known, and the above suggestions are speculative.

A potential concern with etanercept was increased susceptibility to infection or decreased resistance to infection. Although there was a trend toward increased infections in patients in RECOVER, this was not observed in RENAISSANCE, wherein the patients were treated for longer periods of time. Moreover, there was no significant increase in serious infections in either trial (Table 4). Of note, no

## TABLE 3. Adverse Events Reported by ≥5% of Patients in RECOVER and RENAISSANCE

<table>
<thead>
<tr>
<th>Event</th>
<th>RECOVER (n=1123)</th>
<th>RENAISSANCE (n=925)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=373)</td>
<td>Etanercept QW (n=375)</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>45 (12.1)</td>
<td>58 (15.5)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>24 (6.4)</td>
<td>15 (4.0)</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>16 (4.3)</td>
<td>19 (5.1)</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>28 (7.5)</td>
<td>44 (11.7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (1.3)</td>
<td>5 (1.3)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>20 (5.4)</td>
<td>21 (5.6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>24 (6.4)</td>
<td>17 (4.5)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>20 (5.4)</td>
<td>20 (5.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>22 (5.9)</td>
<td>20 (5.3)</td>
</tr>
<tr>
<td>Cough increased</td>
<td>20 (5.4)</td>
<td>17 (4.5)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12 (3.2)</td>
<td>24 (6.4)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>3 (0.8)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (0.8)</td>
<td>10 (2.7)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>30 (8.0)</td>
<td>35 (9.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>RENAISSANCE (n=925)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M Placebo (n=307)</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>80 (26)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>49 (16)</td>
</tr>
<tr>
<td>Headache</td>
<td>36 (12)</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>37 (12)</td>
</tr>
<tr>
<td>Injection-site reaction†</td>
<td>16 (5)</td>
</tr>
<tr>
<td>Anemia†</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>37 (12)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>24 (8)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>20 (7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>52 (17)</td>
</tr>
<tr>
<td>Cough increased</td>
<td>28 (9)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13 (4)</td>
</tr>
<tr>
<td>Hyperkalemia†</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Constipation†</td>
<td>21 (7)</td>
</tr>
<tr>
<td>Bronchitis†</td>
<td>34 (11)</td>
</tr>
</tbody>
</table>

*P<0.05, Fisher’s exact test combined etanercept vs placebo.

Values are n (%).

Discussion

The clinical trials reported here did not demonstrate a benefit of etanercept in patients with heart failure despite the wealth of preclinical and preliminary clinical data suggesting a therapeutic role for TNF antagonism in this condition. Although the reasons for this lack of benefit of etanercept are patients in RECOVER, although this was not observed in RENAISSANCE. There was not an increase in serious infections in either study.
significant increase in infections has been seen in randomized controlled trials with etanercept in patients with rheumatoid arthritis and psoriasis. Adverse events that were observed more frequently and that were statistically significant occurred only in the treatment arm of RENAISSANCE and included injection-site reaction, bronchitis, and constipation.

In conclusion, the results of RENEWAL were sufficiently unfavorable as to rule out a clinically relevant benefit of targeted anticytokine therapy with the soluble TNF antagonist etanercept on the rate of death or CHF hospitalization in CHF. Although one interpretation of the disappointing results of the recent clinical trials with targeted anticytokine therapy in heart failure is that inflammatory mediators are not viable targets in heart failure, a countervailing point of view is that we simply have not targeted proinflammatory mediators with agents that can be used safely in the context of heart failure, or alternatively, that targeting a single component of the inflammatory cascade is not sufficient in a disease as complex as heart failure. Moreover, these studies do not exclude the possibility that there exists a select group of patients in whom TNF antagonism may be beneficial. Whether broader-spectrum anti-inflammatory strategies (eg, statins, immunoadsorption, or immune modulation therapy) will have any added value in heart failure is currently being addressed in ongoing clinical trials.

Appendix

Table 4. Incidence of Infections in RECOVER and RENAISSANCE

<table>
<thead>
<tr>
<th></th>
<th>RECOVER Placebo</th>
<th>Etanercept 25 mg QW</th>
<th>Etanercept 25 mg BIW</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any infection</td>
<td>33</td>
<td>39</td>
<td>40</td>
<td>0.067</td>
</tr>
<tr>
<td>Severe or life-threatening infection</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>0.373</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>RENAISSANCE Placebo</th>
<th>Etanercept 25 mg BIW</th>
<th>Etanercept 25 mg TIW</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any infection</td>
<td>65</td>
<td>68</td>
<td>66</td>
<td>0.824</td>
</tr>
<tr>
<td>Severe or life-threatening infection</td>
<td>10</td>
<td>9</td>
<td>7</td>
<td>0.539</td>
</tr>
</tbody>
</table>

Values are percentages. Data were analyzed with Fisher’s exact test.

Biostatistical Group

Thomas Fleming (University of Washington), David Kerr (AXIO Research Corporation), Ruth McBride (AXIO Research Corporation), Ron Pedersen (Wyeth Research), and Jim Whitmore (Amgen).

Principal Investigators

RECOVER Investigators

Gregor Ahlberg (Falun, Sweden), Maria Cecilia Albanese (Udine, Italy), Jan Aldershivile (Kobenhavn Ø, Denmark), Eduard Allegria (Pamplona, Spain), Vera Ambrovicova (Levice, Slovakia), John Vincent Amerena (Geelong, Victoria, Australia), Bert Andersson (Göteborg, Sweden), Ruta Babarskiene (Kaunas, Lithuania), Noël Baille (Metz Cedex, France), Stellan Bandh (Västerås, Sweden), Robert Barraine (Poitiers Cedex, France), Jens Berning (Aalborg, Denmark), Jose Ramón Berrazuela (Santander, Spain), Egidijus Berukstis (Vilnius, Lithuania), Kurt Boman (Skellefteå, Sweden), Jean Bour (St. Avold Cedex, France), Angelo Branzi (Bologna, Italy), Jordi Bruguera (Barcelona, Spain), Manuel Oliveira Carrageta (Almada, Portugal), Avraham Caspi (Rehovot, Israel), Antonia Amaro Cendon (A Coruña, Spain), Zuzka Chati (Essex Les Nanc, France), J.H. Cornel (Alkmaar, The Netherlands), David Cross (Auchenflower, Queensland, Australia), Arturo Fernandez Cruz (Madrid, Spain), Saenz Cusi (Barcelona, Spain), Morten Gundtvand Dahlé (Lillehammer Fylkeskommune, Norway), Ulf Dahlstrom (Linköping, Sweden), Thomas Drawin (Saint Die, France), Helmut Drexler (Hannover, Germany), Andrezej Dubinski (Walbrzych, Poland), Kennet Egstrup (Svendborg, Denmark), Jerónimo Farre (Madrid, Spain), Roberto Ferrari (Ferrara, Italy), Charles Mark Francis (Kircaldy, United Kingdom), A. Galbraith (Chersmade, Queensland, Australia), Michel Galinier (Toulouse Cedex, France), Enrique Galve (Barcelona, Spain), Pantaleo Giannuzzi (Veruno [Novara], Italy), M. Goethals (Aalst, Belgium), Jacek Gorski (Gdynia, Poland), Robert Greenbaum (Middlesex, United Kingdom), Peter H. Groves (Cardiff, United Kingdom), Markus Haass (Heidelberg, Germany), Torben Helge Haghfelt (Odense C, Denmark), Henryk Halacziewicz (Starachowice, Poland), Angus Hamer (Box Hill, Victoria, Australia), Silvia Hansone (Riga LV, Latvia), Ilona Hegyi (Vasvari, Hungary), Per Hildebrandt (Frederiksberg, Denmark), Christo Höglund (Stockholm, Sweden), Laurence Howes (Kogarah, New South Wales, Australia), I. Hudson (Leicester, United Kingdom), Matti Huttunen (Savonlinna, Finland), Bruce Jackson (Epping, Victoria, Australia), Ashok Jacob (Livingstone, United Kingdom), Jytte Jensen (Glostrup, Denmark), Janis Jurgenson (Riga LV, Latvia), Christopher Jones (Glamorgan, United Kingdom), J.H. Kadr (Essex, United Kingdom), Thomas Kahan (Danderyd, Sweden), Pål Kárpáti (Budapest, Nyggynasar, Hungary), Julius Kasper (Bratislava, Slovakia), Per Katzman (Helsingborg, Sweden), Elsadig Kazzam (Eskilstuna, Sweden), Anne M. Keogh (Darlinghurst, New South Wales, Australia), Khaifele Khaifele (Metz Cedex, France), Kai Killavuori (Espoo, Finland), Lars Kåber (Hellerup, Denmark), Jaspal S. Kooner (Southall, Middlesex, United Kingdom), Jerzy Korewicki (Warszawa, Poland), R. Körfer (Bad Oeynhausen, Germany), J.A. Kragnet (Heerlen, The Netherlands), Thomas Kronvall (Örebro, Sweden), Henry Krum (Prahran, Victoria, Australia), Maria Krzemsinska-Pakula (Lodz, Poland), Krzystof Kuc (Zielona Gora, Poland), Gyula Kurta (Berettyoujfalu, Orban, Hungary), Jean Marc Lablanche (Lille Cedex, France), Finn Landgren (Kalmar, Sweden), Geoffrey Lane (Freemantle, West Australia, Australia), Aleksandras

Committees

RENEMENT Steering Committee

K. Swedberg (Co-Chair), M. Packer (Co-Chair), J. McMurray, D. Mann, M. Warren (Amgen Corporation representative), and B. Riggs (Wyeth Research representative).

RECOVER Steering Committee


RENAISSANCE Steering Committee

D. Mann (Chair), J. Borer, W. Colucci, A. Feldman, P. Liu, M. Packer, and M. Warren (Amgen Corporation representative).

End-Points Committee


Data Monitoring and Safety Board

RENASSANCE Investigators

Jonathan Abrams (Albuquerque, NM), Kirkwood Adams (Chapel Hill, NC), Inder Anand (Minneapolis, Minn),
J. Malcolm Arnold (London, ON, Canada), Deborah Asheim (New York, NY), Alan Bank (St. Paul, Minn), Raye Lynn Bellinger (Sacramento, Calif), James Bergin (Charlottesville, Va), Victoria Bernstein (Vancouver, BC, Canada), Girish Bhaskar (Lake City, Fla), Philip Binkley (Columbus, Ohio), John Boehmer (Hershey, Pa),
Robert Bourge (Birmingham, Ala), Doug Chapman (Ottawa, ON, Canada),
Teresa DeMarco (San Francisco, Calif), Vincent DeQuattro (Los Angeles, Calif), Thomas DiSalvo (Boston, Mass), Eric Eichhorn (Dallas, Tex), Howard Eisen (Philadelphia, Pa), R. Douglas Easley (Tulsa, Okla), Arthur Feldman (Pittsburgh, Pa),
Daniel Fishbein (Seattle, Wash),
Michael Fowler (Stanford, Calif), Jalal Ghalii (Shreveport, La),
Mihai Gheorghiaie (Chicago, Ill), E. Gilbert (Salt Lake City, Utah),
Thomas Giles (New Orleans, La), Michael Givertz (Baltimore, Md),
Stephen Gottlieb (Baltimore, Md), Barry Greenberg (San Diego, Calif),
Stephen Halpern (Santa Rosa, Calif), Joshua Hare (Baltimore, Md),
Grady Hendrix (Charleston, SC), Ray Hershberger (Portland, Ore),
Michael Higginbotham (Durham, NC), James Hill (Gainesville, Fla),
Clare Hohreiter (New York, NY), Debra Issac (Calgary, Alberta, Canada),
Mariell Jessup (Philadelphia, Pa), Jill Kalman (New York, NY),
Ronald Karlberg (Beverly Hills, Calif), Marc Kates (Phoenix, Ariz), Andrew Keller (Fairfax, Va),
Dean Kereiakes (Cincinnati, Ohio),
Marc Klapolch (New York, NY), Michael Koren (Jacksonville, Fla),
Greg Koshkarian (Tucson, Ariz), Steven Krueger (Lincoln, Neb),
Merrick Kukin (New York, NY), Robin Kuritzky (Vancouver, British Columbia, Canada),
Charles Lanzarotti (Milwaukee, Wis), Joseph Lash (Louisville, Ky),
Richard Lee (Scottsdale, Ariz),
Wayne Leimbach (Tulsa, Okla), Thierry Lefemite (Brock, NY),
T. Barry Levine (Farmington Hills, Mich), Chang-seng Liang (Rochester, NY),
Peter Liu (Toronto, Ontario, Canada),
Irving Loh (Thousand Oaks, Calif), Alan Maisel (San Diego Calif),
Douglas Mann (Houston, Tex),
Frank McGrew (Memphis, Tenn),
Robert McKelvie (Hamilton, Ontario, Canada),
Edward McMillan (Charlotte, NC),
Alan Miller (Jacksonville, Fla),
Leslie Miller (Minneapolis, Minn),
Gordon Moe (Toronto, Ontario, Canada),
Sayed Mohiuddin (Ottawa, Neb),
David Murray (San Antonio, Tex),
Imran Nazir (Baltimore, Md),
John Nicklas (Ann Arbor, Mich),
Joseph O’Brien (Fl, Myers, Fla),
Robert Oerlemans (Lake City, Iowa),
Robert Palac (Lebanon, NH), Gregory Pennock (Tucson, Ariz),
Charles Porter (Kansas City, Mo),
Steven Profomishoff (Hillsboro, Ore),
Normand Racine (Montreal, Quebec, Canada),
Hilfer Ribiner (Newark, NJ),
Jonathan Sackner-Bernstein (New York, NY),
John Schmedtje (Reno, Neva),
Douglas Schoken (Tampa Fla),
Marc Silver (Oak Lawn, Ill),
Eugene Smith (Little Rock, Ark),
Andrew Smith (Atlanta, Ga),
Maureen Smithers (Colorado Springs, Colo),
David Stagaman (Spokane, Wash),
 Allan Stahl (Beverly Hills, Calif),
Robert Stolaroff (Baltimore, Md),
David Stower (New Orleans, La),
Michael Sullivan (Boston, Mass),
Robert Sznajderman (Hartford, Ct),
Norman Suskind (San Francisco, Calif),
William Talar (Phoenix, Ariz),
Keith Talley (Birmingham, Ala),
Robert Thompson (Baltimore, Md),
Barbara Tinzl (Cincinnati, Ohio),
Kerry Torii (Denver, Co),
Barbara Traupman (St Louis, Mo),
Daniel Trimble (Atlanta, Ga),
Caroline Turek (Denver, Co),
David Uber (El Paso, Tex),
Michael Uehling (Portland, Me),
Richard Urrutia (Baltimore, Md),
Barbara Vail (Baltimore, Md),
Robert Valente (Rochester, NY),
Tim Van Dyke (Indianapolis, Ind),
David Van Hook (Washington, D.C),
Sandra Varner (Minneapolis, Minn),
Wendy Vazquez (New Orleans, La),
Daniel Veldhuizen (Minneapolis, Minn),
Mark Vickers (Toronto, Ontario, Canada),
John Vliet (Nashville, Tenn),
Robert Volpe (San Diego, Calif),
Gautam Vora (San Francisco, Calif),
Mark Wagle (Gainesville, Fla),
Kari Walker (Gainesville, Fla),
Barbara Warfield (Seattle, Wa),
Robert Weiss (San Francisco, Calif),
John Weinberg (San Francisco, Calif),
Mary Welke (Salt Lake City, Utah),
Jere Westin (Los Angeles, Calif),
Susan Whitehead (Baltimore, Md),
Nancy Whitehouse (Denver, Co),
Charles Whelan (Houston, Tex),
Robert Wiener (North Hollywood, CA),
Karen Williams (San Francisco, Calif),
David Wilson (Columbia, Mo),
John Winters (Phoenix, Ariz),
Richard Wissler (Minneapolis, Minn),
Kevin Wood (Baltimore, Md),
Robert Wright (Seattle, Wa),
David Wu (San Francisco, Calif),
Brett Yamanaka (Boulder, Co),
William Yellin (Salt Lake City, Utah),
Lisa Yodfat (San Diego, Calif),
Robert Zillman (Baltimore, Md),
Barbara Zierler (Salt Lake City, Utah),
Martin Zisk (San Francisco, Calif),
Mark Zimmerman (San Francisco, Calif),
Robert Zonies (Portland, Me),
John Zuckerman (Boston, Mass),
William Zuelke (Salt Lake City, Utah),
E. Gilbert (Salt Lake City, Utah),
Thomas Giles (New Orleans, La),
Michael Givertz (Baltimore, Md),
Stephen Gottlieb (Baltimore, Md),
Barry Greenberg (San Diego, Calif),
Stephen Halpern (Santa Rosa, Calif), Joshua Hare (Baltimore, Md),
Grady Hendrix (Charleston, SC), Ray Hershberger (Portland, Ore),
Michael Higginbotham (Durham, NC), James Hill (Gainesville, Fla),
Clare Hohreiter (New York, NY), Debra Issac (Calgary, Alberta, Canada),
Mariell Jessup (Philadelphia, Pa), Jill Kalman (New York, NY),
Ronald Karlberg (Beverly Hills, Calif), Marc Kates (Phoenix, Ariz),
Andrew Keller (Fairfax, Va),
Dean Kereiakes (Cincinnati, Ohio),
Marc Klapolch (New York, NY),
Michael Koren (Jacksonville, Fla),
Greg Koshkarian (Tucson, Ariz),
Steven Krueger (Lincoln, Neb),
Merrick Kukin (New York, NY),
Robin Kuritzky (Vancouver, British Columbia, Canada),
Charles Lanzarotti (Milwaukee, Wis),
Joseph Lash (Louisville, Ky),
Richard Lee (Scottsdale, Ariz),
Wayne Leimbach (Tulsa, Okla),
Thierry Lefemite (Brock, NY),
T. Barry Levine (Farmington Hills, Mich),
Chang-seng Liang (Rochester, NY),
Peter Liu (Toronto, Ontario, Canada),
Irving Loh (Thousand Oaks, Calif),
Alan Maisel (San Diego Calif),
Douglas Mann (Houston, Tex),
Frank McGrew (Memphis, Tenn),
Robert McKelvie (Hamilton, Ontario, Canada),
Edward McMillan (Charlotte, NC),
Alan Miller (Jacksonville, Fla),
Leslie Miller (Minneapolis, Minn),
Gordon Moe (Toronto, Ontario, Canada),
Sayed Mohiuddin (Ottawa, Neb),
David Murray (San Antonio, Tex),
Imran Nazir (Baltimore, Md),
John Nicklas (Ann Arbor, Mich),
Joseph O’Brien (Fl, Myers, Fla),
Robert Oerlemans (Lake City, Iowa),
Robert Palac (Lebanon, NH),
Gregory Pennock (Tucson, Ariz),
Charles Porter (Kansas City, Mo),
Steven Profomishoff (Hillsboro, Ore),
Normand Racine (Montreal, Quebec, Canada),
Hilfer Ribiner (Newark, NJ),
Jonathan Sackner-Bernstein (New York, NY),
John Schmedtje (Reno, Neva),
Douglas Schoken (Tampa Fla),
Marc Silver (Oak Lawn, Ill),
Eugene Smith (Little Rock, Ark),
Andrew Smith (Atlanta, Ga),
Maureen Smithers (Colorado Springs, Colo),
David Stagaman (Spokane, Wash),
 Allan Stahl (Las Vegas, Nev),
Alan Steller (Las Vegas, Nev),
John Strobeck (Hawthorne, NJ),
James Tam (Winnipeg, Manitoba, Canada),
John Teerlink (San Francisco, Calif),
Udho Thadani (Oklahoma City, Okla),
Robert Tobar (Vero Beach, Fla),
Guillermo Torre (Houston, Tex),
Condon Vander Ark (Madison, Wis),
Lynne Wagoner (Cincinnati, Ohio),
John Wilson (Nashville Tenn),
Richard Wright (Santa Monica, Calif),
Clyde Yance Jr (Dallas, Tex),
and James Young (Cleveland Ohio).

Acknowledgments

The RENASSANCE and RECOVER trials were funded by Amgen Inc (Amgen Corporation), Thousand Oaks, Calif, and Wyeth Research, Collegeville, Pa. The authors would like to thank the following individuals for assistance with preparation of the manuscript: Ann Dugan, Margaret Summersgill, and Jim Whitemore (Amgen) and Evan Loh, Debra Marshall, Maureen Murphy, Ron Pedersen, Scott Saunders, and Donna Simco (Wyeth Research)
References
Targeted Anticytokine Therapy in Patients With Chronic Heart Failure: Results of the Randomized Etanercept Worldwide Evaluation (RENEWAL)


_Circulation_. 2004;109:1594-1602; originally published online March 15, 2004; doi: 10.1161/01.CIR.0000124490.27666.B2

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/109/13/1594

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/