Case Reports of Heart Failure after Therapy with a Tumor Necrosis Factor Antagonist

Hyon J. Kwon, PharmD, MPH; Timothy R. Coté, MD, MPH; Michael S. Cuffe, MD; Judith M. Kramer, MD, MS; and M. Miles Braun, MD, MPH

Background: Etanercept and infliximab are U.S. Food and Drug Administration-approved tumor necrosis factor (TNF) antagonists.

Objective: To describe adverse event reports of heart failure after TNF antagonist therapy.

Design: Case series.

Setting: The U.S. Food and Drug Administration’s MedWatch program.

Patients: 47 patients who developed new or worsening heart failure during TNF antagonist therapy.

Measurements: Clinical and laboratory reports.

Results: After TNF antagonist therapy, 38 patients developed new-onset heart failure and 9 patients experienced heart failure exacerbation. Of the 38 patients with new-onset heart failure, 19 (50%) had no identifiable risk factors. Ten patients younger than 50 years of age developed new-onset heart failure after receiving TNF antagonists. After TNF antagonist therapy was discontinued and heart failure therapy was started in these 10 patients, 3 had complete resolution of heart failure, 6 improved, and 1 died.

Conclusion: In a fraction of patients, TNF antagonists might induce new-onset heart failure or exacerbate existing disease.


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METHODS

The FDA’s MedWatch program receives reports of adverse events related to FDA-licensed products after the products are marketed to the general population (11). Adverse event reports are submitted by manufacturers, physicians, other health care workers, consumers, and others. Except for manufacturers, reporting is voluntary, and the proportion of all adverse events reported to MedWatch is unknown (12). Using the high-level group term heart failure from the Medical Dictionary for Regulatory Activities, we searched MedWatch records for adverse event reports of heart failure among patients receiving etanercept or infliximab from the time of licensure through February 2002. We included both patients with new-onset heart failure and patients with exacerbation of preexisting heart failure after administration of a TNF antagonist. We excluded heart failure reports that were temporally associated with other heart failure–initiating events (such as myocardial infarction, infection, pulmonary embolism, or atrial fibrillation). A cardiologist reviewed each report and determined that the available evidence supported the diagnosis of heart failure. Since patients younger than 50 years of age are relatively unlikely to develop heart failure due to traditional risk factors (that is, coronary artery disease, hypertension, and valvular abnormalities), we contacted reporting physicians of patients younger than 50 years of age to collect information on predisposing factors, tests of left ventricular function (for example, echocardiography), and clinical course and outcome. The funding sources had no role in the design, conduct, or reporting of this study.

More than a decade ago, Levine and colleagues (1) demonstrated increased serum levels of tumor necrosis factor (TNF) in patients with advanced heart failure. Torre-Amione and colleagues (2) later showed that TNF levels correlated with the severity of heart failure. Other experimental findings (3, 4) supported the role of TNF in heart failure, and early clinical studies of blocking TNF in patients with heart failure demonstrated promising results (5–7). However, large-scale randomized, placebo-controlled trials of etanercept for treatment of heart failure were stopped early because they failed to demonstrate an improvement in clinical heart failure or mortality (8). A phase II trial in 150 patients (101 taking infliximab and 49 taking placebo) who had New York Heart Association class III to IV heart failure showed excess mortality (7 deaths vs. 0 deaths) and hospitalization for worsening heart failure in the infliximab group (9).

At the time of our study, two TNF antagonists, etanercept and infliximab, were approved for use in the United States. Etanercept (Amgen, Thousand Oaks, California) is a recombinant, soluble TNF type 2 receptor that binds and inhibits TNF and is used to treat rheumatoid, juvenile rheumatoid, and psoriatic arthritis. Infliximab (Centocor, Malvern, Pennsylvania) is a chimeric monoclonal antibody against TNF-α and is used to treat Crohn disease and, in combination with methotrexate, rheumatoid arthritis. Neither product is indicated for the prevention or treatment of heart failure. As of July 2001, 104,000 patients had been treated with etanercept and 170,000 patients had been treated with infliximab worldwide (10). Because controlled trials in patients with heart failure showed no benefit of TNF antagonists and, in the case of the infliximab trial, suggested worse outcome, we examined spontaneous adverse event reports to the U.S. Food and Drug Administration’s MedWatch system for evidence that TNF antagonists can exacerbate heart failure or promote new-onset heart failure.
RESULTS

Forty-seven patients had heart failure after receiving TNF antagonists. Thirty-eight (81%) developed new-onset heart failure, and 9 (19%) experienced heart failure exacerbations (Table 1). The median age was 62 years (range, 19 to 87 years) for patients with new-onset heart failure and 70 years (range, 57 to 74 years) for patients with heart failure exacerbation. Twenty-eight of 38 patients who developed new-onset heart failure (74%) were age 50 years or older. Twenty-nine of 38 patients with new-onset heart failure (76%) and all patients with heart failure exacerbation were receiving a TNF antagonist for rheumatoid arthritis. Of the 38 patients who reported new-onset heart failure, 19 (50%) had no identifiable traditional risk factor for heart failure (previous myocardial infarction, coronary heart disease, hypertension, or diabetes). The median interval from the first dose of TNF antagonist to a diagnosis of new-onset heart failure or heart failure exacerbation was 3.5 months (range, 24 hours to 24 months) and 4 months (range, 24 hours to 20 months), respectively.

All 10 patients younger than 50 years of age (range, 19 to 48 years of age) developed new-onset heart failure after

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Table 1. Summary Characteristics of Heart Failure Reported with Use of Tumor Necrosis Factor Antagonists*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>New-Onset Heart Failure without Documented Risk Factors</th>
<th>New-Onset Heart Failure with Documented Risk Factors</th>
<th>Heart Failure Exacerbation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>19</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Age, y</td>
<td>Range 19–75</td>
<td>29–87</td>
<td>57–74</td>
</tr>
<tr>
<td></td>
<td>Median 59</td>
<td>67</td>
<td>70†</td>
</tr>
<tr>
<td>Sex, n</td>
<td>Male 5</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Female 14</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Risk factor for heart failure, n</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease‡</td>
<td>175</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indication, n</td>
<td>Rheumatoid arthritis 15↑</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Crohn disease¶</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psoriatic arthritis</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Juvenile rheumatoid arthritis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Therapy, n</td>
<td>Etanercept 12</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Infliximab 7</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Concomitant therapy, n**</td>
<td>8††</td>
<td>10††</td>
<td>5</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>8††</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Time to event</td>
<td>Range 24 h–24 mo</td>
<td>36 h–14 mo</td>
<td>24 h–20 mo</td>
</tr>
<tr>
<td></td>
<td>Mean 6 mo§§</td>
<td>5.5 mo</td>
<td>7.5 mo§§</td>
</tr>
<tr>
<td></td>
<td>Median 2.5 mo§§</td>
<td>4 mo</td>
<td>4 mo§§</td>
</tr>
<tr>
<td>Death from heart failure, n</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Among 47 patients, 43 were from the United States and 1 patient each was from Switzerland, Ireland, Canada, and Thailand. NA = not applicable.
† In 8 patients.
‡ Coronary heart disease, history of myocardial infarction, hypertension, valvular disease, cardiomyopathy, or arrhythmias.
§ Three patients had concomitant diabetes.
↑ One patient had both rheumatoid arthritis and Crohn disease.
¶ The ages of the 6 patients with Crohn disease were 19 years, 34 years, 40 years, 61 years, 67 years, and 78 years.
** Concomitant therapy for which heart failure has been reported as a possible outcome; however, the patients had taken these agents over the long term.
†† Two patients were also receiving concomitant therapy with nonsteroidal anti-inflammatory drugs.
§§ In 18 patients.
|| In 7 patients.

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Context

Although tumor necrosis factor (TNF) antagonists were once considered as a possible treatment for heart failure, recent trials showed no benefit, and one trial showed worsening heart failure with TNF antagonist treatment.

Contribution

This analysis of data from the U.S. Food and Drug Administration’s MedWatch program on 47 patients who developed heart failure while receiving long-term TNF antagonist therapy showed that 81% had never experienced heart failure before taking TNF antagonists. Half of the patients with new-onset heart failure had no identifiable heart failure risk factors, and 10 patients were younger than 50 years of age.

Implications

Clinicians should be aware that heart failure may occur in patients receiving TNF antagonists.

–The Editors
**Table 2. Characteristics of New-Onset Heart Failure in Patients Younger Than 50 Years of Age***

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Indication</th>
<th>Time to Heart Failure Onset</th>
<th>Signs and Symptoms at Presentation</th>
<th>Evidence of Heart Failure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>Female</td>
<td>Crohn disease</td>
<td>24 h</td>
<td>Dyspnea</td>
<td>Severe left ventricular failure with EF of 0.2 on echocardiography; septal dyskinesia, elevated pulmonary artery pressure, grade 3 mitral incompetence</td>
<td>Complete resolution of heart failure; no clinical signs of heart failure 2.5 months later</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>Female</td>
<td>Juvenile RA</td>
<td>2 wk</td>
<td>Shortness of breath, fatigue, lower-extremity edema, pleural effusion</td>
<td>EF of 0.1, nonischemic heart failure, mild increase in pulmonary pressure consistent with heart failure seen on cardiac catheterization</td>
<td>Improvement of cardiac function and resolution of pulmonary edema with diuresis; EF of 0.3 at follow-up</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>Male</td>
<td>Crohn disease</td>
<td>3 mo</td>
<td>Shortness of breath, dyspnea, tachycardia</td>
<td>Pulmonary edema on chest radiography, LVEF &lt;0.4 on echocardiography</td>
<td>Improved with heart failure treatment; 2 days later, developed recurrence of heart failure signs and symptoms; died suddenly in sleep 4 days later</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>Male</td>
<td>Crohn disease</td>
<td>4 mo</td>
<td>Neck vein distension, dyspnea on exertion, paroxysmal nocturnal dyspnea, S3 gallop, rales</td>
<td>LVEF of 0.1 on echocardiography; cardiomegaly, pulmonary edema, and “grade 2 CHF changes” on chest radiography; evidence of left ventricular hypertrophy on ECG</td>
<td>Improved with heart failure treatment</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>Male</td>
<td>RA and Crohn disease</td>
<td>4 mo</td>
<td>Shortness of breath, dyspnea on exertion, palpitation, blood pressure of 170/80 mm Hg</td>
<td>Dilated left ventricle, EF of 0.3, and aortic, mitral, and tricuspid regurgitation on echocardiography; T-wave inversion in lateral leads with left ventricular hypertrophy on ECG; cardiomegaly on chest radiography</td>
<td>Improved with heart failure treatment</td>
</tr>
<tr>
<td>6†</td>
<td>48</td>
<td>Female</td>
<td>RA</td>
<td>6 mo</td>
<td>Neck vein distension, dyspnea on exertion, paroxysmal nocturnal dyspnea, S3 gallop, rales, mild pitting edema of both legs</td>
<td>EF of 0.45, left ventricular enlargement, right atrial enlargement, hypokinesis of septum and basal anterior segment on echocardiography; cardiomegaly with pulmonary congestion on chest radiography</td>
<td>Improved with heart failure treatment</td>
</tr>
<tr>
<td>7†</td>
<td>29</td>
<td>Female</td>
<td>RA</td>
<td>8 mo</td>
<td>Peripheral edema, neck vein distention, dyspnea on exertion, orthopnea, S3 gallop</td>
<td>EF of 0.35 to 0.4, left ventricular hypertrophy, mitral regurgitation on echocardiography</td>
<td>Improved with heart failure treatment</td>
</tr>
<tr>
<td>8†</td>
<td>29</td>
<td>Male</td>
<td>Psoriatic arthritis</td>
<td>5 mo</td>
<td>Dyspnea on exertion that progressed to dyspnea at rest, ankle edema</td>
<td>EF of 0.18, biventricular failure, dilated cardiomyopathy, trace mitral regurgitation on echocardiography; cardiomegaly on chest radiography</td>
<td>Improved with heart failure treatment; EF improved to 0.29 approximately 2 years later</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>Female</td>
<td>RA</td>
<td>9 mo</td>
<td>Nausea, vomiting, chest pain</td>
<td>Normal coronary arteries, EF of 0.25 on cardiac catheterization (EF of 0.45 on echocardiography 3 months before the heart failure event), cardiomyopathy</td>
<td>Complete resolution of heart failure; no signs of congestive heart failure and normal EF 2 weeks later</td>
</tr>
<tr>
<td>10</td>
<td>48</td>
<td>Female</td>
<td>RA</td>
<td>17 mo</td>
<td>Shortness of breath</td>
<td>Not available</td>
<td>Complete resolution of heart failure</td>
</tr>
</tbody>
</table>

* CHF = congestive heart failure; ECG = electrocardiography; EF = ejection fraction; LVEF = left ventricular ejection fraction; RA = rheumatoid arthritis.
† History of hypertension.
‡ History of diabetes.
receiving TNF antagonists. Table 2 provides clinical summaries of these cases. Six patients received infliximab, and 4 patients received etanercept. Echocardiography data were obtained in 9 of 10 patients and demonstrated decreased ejection fraction, with a median ejection fraction of 0.2 (range, 0.1 to 0.45); the remaining patient was included on a clinical basis alone. Three patients reported an underlying risk factor for heart failure: Two taking etanercept had diabetes, and 1 taking infliximab had hypertension. The median time to heart failure diagnosis in patients younger than 50 years of age was 3.5 months (range, 24 hours to 6 months) for those who received infliximab and 8.5 months (range, 5 months to 17 months) for those who received etanercept.

Nine of these 10 patients were reported to have discontinued TNF antagonist therapy after heart failure diagnosis. It was not known whether TNF antagonist therapy was discontinued in the remaining patient. Following heart failure treatment, 3 patients reported complete resolution of heart failure, 6 patients reported improvement, and 1 patient died. Three of the 6 patients whose heart failure improved had documented risk factors for heart failure.

**DISCUSSION**

This is one of the first case series of new-onset heart failure temporally associated with TNF antagonists. The cases detailed here, taken together with recent data from clinical trials, suggest that TNF antagonists might induce heart failure in a subset of patients. However, because the incidence and history of heart failure are not well described in the populations receiving these drugs, these spontaneous reports alone are not sufficient to make causal inferences.

Our understanding of the pathophysiology of chronic heart failure has evolved over the past two decades. Although originally thought to be due primarily to hemodynamic derangement, it is now considered a syndrome mostly influenced by activation of the sympathetic nervous system and neurohormonal axis (renin–angiotensin system). Neurohormonal activation initially provides appropriate compensatory mechanisms for an acute decrease in cardiac output, but its long-term consequences are maladaptive.

Inflammatory cytokines, such as TNF, are also overproduced in chronic heart failure and are thought to correspond to a similarly maladaptive inflammatory process (1, 2). However, although elevated circulating TNF levels are noted in patients with severe heart failure and this overproduction appears to be largely cardiac in origin (13), heart failure, unlike arthritis and Crohn disease, is not principally an inflammatory process. The syndrome of heart failure and the systemic response to myocardial injury are complex, with noninflammatory features particularly prominent. The recent failures of infliximab and etanercept (9, 14) to demonstrate benefit in heart failure illustrate this complexity.

It is rare for inflammatory bowel diseases to have cardiovascular effects. However, cardiovascular disease is a recognized extra-articular complication of rheumatoid arthritis, usually due to an increase in premature coronary atherosclerosis or, more rarely, active vasculitis (15). Although we excluded cases of new or worsening heart failure with concomitant myocardial infarction, underlying rheumatoid arthritis or other comorbid conditions may have contributed to heart failure in some older patients.

Finally, it is possible that some of these reported heart failure events occurred by chance. In the general U.S. population, the prevalence of heart failure is reported to be 2% among persons age 40 to 59 years and more than 5% among persons age 60 to 69 years (16). Given the number of persons exposed to TNF antagonist therapy, these prevalence figures suggest that coincidental heart failure among TNF antagonist recipients is a possibility. Nevertheless, the resolution or improvement of heart failure after withdrawal of TNF antagonists and administration of heart failure treatment in 9 younger patients (50 years of age) shows that there may be a causal connection.

Given the underreporting common in spontaneous reporting systems, the cases outlined here may represent only a fraction of actual heart failure events following therapy with TNF antagonists. The FDA continues to solicit reports of this and other adverse drug events from physicians and health care providers, even if causality is uncertain. Care providers can easily report directly to the FDA through the MedWatch program. The form for reporting, available at www.fda.gov/medwatch, is brief and takes approximately 10 to 15 minutes to complete. Timely and complete reports of heart failure in patients receiving TNF antagonists will be important in assessing the extent of this problem.

This case series has important pragmatic implications. Clinicians should be aware that new-onset heart failure or exacerbation of preexisting heart failure may occur in patients who begin TNF antagonist therapy.

From the U.S. Food and Drug Administration, Rockville, Maryland, and Duke Clinical Research Institute, Durham, North Carolina.

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