Effect of Thalidomide on Cardiac Remodeling in Chronic Heart Failure
Results of a Double-Blind, Placebo-Controlled Study

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Background—Inflammation and matrix degradation may play a pathogenic role in chronic heart failure (CHF), and therefore, we examined whether thalidomide, a drug with potential immunomodulating and matrix-stabilizing properties, could improve left ventricular (LV) function in patients with CHF secondary to idiopathic dilated cardiomyopathy (IDCM) or coronary artery disease (CAD).

Methods and Results—Fifty-six patients with CHF and an LV ejection fraction (LVEF) <40% who were already on optimal conventional cardiovascular treatment were randomized to thalidomide (25 mg QD increasing to 200 mg QD) or placebo and followed up for 12 weeks. Our main findings were as follows: (1) During thalidomide treatment but not during placebo, there was a marked increase in LVEF (7 EF units) along with a significant decrease in LV end-diastolic volume and heart rate. (2) This improvement in LVEF was accompanied by a decrease in matrix metalloproteinase-2 without any changes in its endogenous tissue inhibitor, suggesting a matrix-stabilizing net effect. (3) Thalidomide also induced a decrease in total neutrophil count and an increase in plasma levels of tumor necrosis factor-α, suggesting both proinflammatory and antiinflammatory effects. (4) The effect of thalidomide on LVEF was more marked in IDCM than in CAD, possibly partly reflecting that the former group was able to tolerate a higher thalidomide dosage.

Conclusions—Although our results must be confirmed in larger studies that also examine the effects on morbidity and mortality, our findings suggest a role for thalidomide in the management of CHF in addition to traditional cardiovascular medications. (Circulation. 2005;112:3408-3414.)

Key Words: heart failure ■ inflammation ■ leukocytes ■ matrix metalloproteinases ■ remodeling

Despite state-of-the-art cardiovascular treatment, chronic heart failure (CHF) is a progressive disease with high morbidity and mortality, suggesting that important pathogenic mechanisms remain unmodified. We and others have suggested that persistent inflammation may represent such unmodified mechanisms. Thus, several reports have demonstrated enhanced expression of inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, in CHF in direct relation to the deterioration in cardiac performance. Moreover, several studies have suggested that these inflammatory mediators have pathogenic effects on the myocardium by influencing heart contractility, inducing hypertrophy, degrading the matrix, or enhancing fibrosis, thus contributing to the continuous myocardial remodeling process.

The sedative and antinausea drug thalidomide has recently been used as an investigational agent in diseases such as erythema nodosum leprosum, rheumatoid arthritis, and cancer. Moreover, in a recent open pilot study examining a small number of patients, we found improved left ventricular ejection fraction (LVEF) in CHF patients during thalidomide therapy. However, although thalidomide has been shown to have both antiinflammatory and anticancerous properties, the mechanisms of action of thalidomide in various disorders remain unclear, and contradictory results have been reported concerning its effects on cytokine levels in vivo. In addition, other properties related to thalidomide, such as its effects on matrix degradation, could be even more important in relation to its potential beneficial effect in CHF.
Study Population and Study Design

Patients with CHF for >6 months who were admitted to our departments during 2002 to 2003 were consecutively recruited to the study. The inclusion criteria were as follows: (1) clinical CHF of New York Heart Association (NYHA) functional class II and III; (2) LVEF <40%; (3) no changes in medication during the last 3 months; and (4) patients who were clinically and hemodynamically stable, optimally treated with cardiovascular medications, and with no possibility of surgical improvement. The exclusion criteria were as follows: (1) evidence of acute coronary syndromes during the last 6 months; (2) significant concomitant disease, such as infections, pulmonary disease, or collagen vascular disorders; (3) abnormal liver function test results (bilirubin, aspartate aminotransferase, or alanine aminotransferase >2 times the upper limit of normal); (4) women of child-bearing potential; and (5) any form of neuropathy.

The study population consisted of 56 patients (mean age, 66 years; range, 41 to 88; Table 1). The etiology of CHF was coronary artery disease (CAD, n = 38), idiopathic dilated cardiomyopathy (IDCM, n = 17), or valvular disease (n = 1) based on coronary angiographic examination (CAD was defined as at least 1-vessel disease with >75% narrowing of the luminal diameter), echocardiography, and disease history. The study was approved by the regional ethics committee and the Norwegian Medicines Agency. Signed, informed consent was obtained from each patient.

After baseline measurements, the patients were randomly assigned and titrated to a target dosage (200 mg QD) of thalidomide (Sauramide, Penn Pharmaceuticals) or placebo (Penn Pharmaceuticals) as tolerated (starting dosage of 25 mg and doubling every second week). The duration of therapy was 12 weeks.

### Study End Points

The primary end point in the study was changes in LVEF from baseline to week 12 as assessed by ECG-synchronized, gated radionuclide ventriculography at rest (with intra-assay and interassay coefficients of variation <6%). Secondary end points (all regarded as continuous measurements) were changes from baseline to week 12 in: (1) LV end-diastolic volume (LVEDV) and right ventricular ejection fraction (RVEF) as assessed by scintigraphy; (2) clinical evaluation as assessed by NYHA classification and measurements of heart rate (HR) and blood pressure performed by a single, experienced cardiologist; (3) quality of life as assessed by the Minnesota Living With Heart Failure Questionnaire and the McMaster Overall Treatment Evaluation questionnaire; (4) plasma levels of N-terminal brain natriuretic peptide (NT-proBNP); and (5) immunologic variables. Although scintigraphic measurements and quality-of-life assessments were performed only at baseline and after 12 weeks, measurements of immunologic and neurohumoral variables and clinical assessments were also performed after 2 and 4 weeks of follow-up.

### Blood Sampling Protocol

Peripheral venous blood was drawn into pyrogen-free tubes with EDTA as an anticoagulant. The tubes were immediately immersed in melting ice and centrifuged at 2500g for 20 minutes within 20 minutes. All samples were stored at −80°C and thawed only once.

### Enzyme Immunoassays

TNF-α and IL-10 were measured by enzyme immunoassays (EIAs; Biosource Internationale). IL-8, soluble TNF receptor type I (sTNF-R1), MMP-2, and tissue inhibitor of MMP (TIMP)-1 were measured by EIAs obtained from R&D Systems. Plasma levels of norepinephrine were measured by EIA according to the extraction protocol provided by the manufacturer (DLD Diagnostica GmbH). The intra-assay and interassay coefficients of variation were <10% for all EIAs. The analyses were batched; ie, all analyses for each parameter were performed on the same day, and all samples from a given patient were analyzed on the same microtiter plate to minimize run-to-run variability.

### Statistical Analysis

The primary objective of the statistical analysis was to compare the effect of thalidomide versus placebo in CHF patients on changes in LVEF between enrolment and 12 weeks. We estimated the required sample size to be 40 patients for a 2-tailed significance level of 0.05 and a power of 0.80 to determine an increase in LVEF of 6% but actually enrolled 56 patients to compensate for possible dropouts. Differences between groups, including baseline comparability between the 2 treatment groups, were compared with Student’s t test or the Mann-Whitney U test for unpaired data. When comparing the subjects’ follow-up changes from their baseline values, Wilcoxon’s signed-rank test was used. When >2 time points were compared (eg, immunologic variables), a multivariate ANOVA was performed a priori, and if significant, Wilcoxon’s signed-rank test for paired data was performed a posteriori. Relations between variables were tested with Spearman’s rank-correlation test. Adverse event rates were compared by using the χ2 test. For variables with >2 measurements (all except scintigraphic measurements and quality-of-life assessment), the data were analyzed on the intention-to-treat principle and by carrying forward the last value for patients who withdrew from the study for any reason. Results are reported as mean ± SEM, and changes in variables after therapy are expressed as the mean and 95% confidence interval (95% CI) unless stated otherwise. Probability values were 2 sided and considered significant when <0.05.

### TABLE 1. Baseline Characteristics of CHF Patients Participating in the Study

<table>
<thead>
<tr>
<th>Medication, n (%)</th>
<th>Thalidomide (n = 28)</th>
<th>Placebo (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67 ± 2.0</td>
<td>65 ± 1.8</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>20/8</td>
<td>22/6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.5 ± 0.6</td>
<td>26.1 ± 0.7</td>
</tr>
<tr>
<td>Cause of heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>21 (71)</td>
<td>17 (61)</td>
</tr>
<tr>
<td>IDCM</td>
<td>7 (29)</td>
<td>10 (36)</td>
</tr>
<tr>
<td>Valvular</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Duration of heart failure, y</td>
<td>4.7 ± 0.7</td>
<td>3.5 ± 0.7</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>24.9 ± 1.6</td>
<td>25.5 ± 1.9</td>
</tr>
</tbody>
</table>

Values are mean ± SEM or n (%). ACE indicates angiotensin-converting enzyme.
Results

The key demographic characteristics and clinical signs were similar in the 2 treatment groups (Table 1). The total eligible, total recruited, and total evaluated patients are shown in Figure 1. Six patients (all in the CAD group) stopped the study medication during thalidomide therapy (1 sudden death and 5 because of exanthema [n=1], increasing dyspnea [n=2], syncope [n=1], and fatigue and constipation [n=1]), whereas 2 patients stopped the study medication during placebo treatment (myocardial infarction in 1 and headache in 1) (P=0.13). Of those who completed the study, 13 (56%) patients on thalidomide and 25 (93%) patients on placebo treatment achieved the goal of 200 mg QD. The mean daily dosage at the end of the study was 146±14 and 193±5 mg in the thalidomide and placebo group, respectively (P<0.001). During the study period, there were no changes in cardiovascular medications in either the thalidomide or the placebo group.

Effect of Thalidomide on Ventricular Function, Hemodynamic and Neurohumoral Responses, and Functional Status

LVEF significantly increased (~7 EF units) during thalidomide treatment, whereas no changes were seen in the placebo group, resulting in a significant difference in changes between the 2 treatment groups (Figure 2 and Table 2). In contrast, the difference in changes for RVEF did not reach statistical significance (Table 2). Thalidomide but not placebo induced a significant decrease in LV volume as measured by LVEDV, resulting in a significant difference between the changes in the 2 treatment groups (Table 2). These changes in myocardial function during thalidomide therapy were accompanied by a significant decrease in HR, whereas no changes were observed during placebo treatment (Table 2). Simultaneously, there were no changes in the PR interval, QRS complex, or QT duration during either thalidomide or placebo therapy, indicating that the decrease in HR during thalidomide treatment was not caused by atrioventricular block, bundle branch block, or a prolonged QT interval. Moreover, although there was a significant decline in HR during thalidomide therapy, there were no changes in norepinephrine levels during either thalidomide or placebo treatment, suggesting that the effect on HR was not secondary to a decline in that neurohormone (Table 2). In contrast to the changes in EF and HR, plasma levels of NT-proBNP, blood pressure, NYHA classification, and quality of life remained unchanged in both treatment groups (Table 2).

The study was originally not designed as an intention-to-treat study because of the lack of clinical parameters as primary end points; for LVEF, there were no measurements between baseline and the end of the study. Thus, although the LVEF data showed a significant difference in changes between the 2 treatment groups, when the data were also analyzed on the intention-to-treat principle (P<0.03), use of the baseline value as the last value carried forward in this model was a significant limitation.

Effect of Thalidomide in Relation to the Etiology of CHF

Although thalidomide markedly improved LVEF in those with IDCM (n=7; increase from 19.9±1.5 to 35.0±4.0 EF units, P<0.01), there was a more modest and nonsignificant increase in those patients with CHF secondary to CAD (n=15; increase from 25.6±2.1 to 29.2±3.0 EF units, P=0.2; Figure 2). In contrast, the effect of thalidomide on RVEF, LVEDV, and HR was independent of the etiology of CHF. The inclusion of unrecognized myocarditis could have been a potential confounder in the IDCM group. However, the fact that the placebo group showed a similar pattern for LVEF in both CAD and IDCM (Figure 2), that all patients had been in a stable clinical and hemodynamic situation for >3 months, and that none of the patients had elevated troponin levels suggests that the IDCM group did not include such patients.

Effect of Thalidomide on Immunologic Parameters

Although the total number of leukocytes significantly decreased during thalidomide treatment, no change was observed during placebo, resulting in a near-significant difference in changes (P=0.06; Table 3). The effect of thalidomide...
Moreover, plasma levels of the antiinflammatory cytokine IL-10 significantly decreased during thalidomide treatment, but not during placebo, further suggesting inflammatory net effects during thalidomide therapy (Table 3).

As shown in Figure 3, most of the changes in TNF-α levels and neutrophil counts during thalidomide therapy were seen within the first 4 weeks, and a similar pattern was also seen for the other immunologic variables (data not shown).

### Effect of Thalidomide on Matrix-Degrading Enzymes
Enhanced MMP activity, also involving MMP-2, seems to play an important pathogenic role in myocardial remodeling in CHF. Interestingly, thalidomide treatment, but not placebo, significantly reduced plasma levels of MMP-2 (Table 3). Moreover, although TIMP-1 significantly decreased during placebo, no changes were seen in the thalidomide group, suggesting inhibitory net effects on MMP activity during thalidomide therapy (Table 3).

### TABLE 2. Clinical and Hemodynamic Variables Before and After 12 Weeks of Therapy With Thalidomide or Placebo

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 Weeks</th>
<th>Change</th>
<th>Baseline</th>
<th>6 Months</th>
<th>Change</th>
<th>Differences in Changes Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class</td>
<td>2.2±0.1</td>
<td>2.3±0.1</td>
<td>0.1 (−0.2, 0.3)</td>
<td>2.2±0.1</td>
<td>2.3±0.1</td>
<td>0.0 (−0.1, 0.2)</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>23.5±1.7</td>
<td>31.6±2.6</td>
<td>7.2 (29, 12.7)$†$</td>
<td>25.5±1.9</td>
<td>24.8±1.8</td>
<td>−0.3 (−2.3, 1.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RVEF, %</td>
<td>38.0±2.2</td>
<td>41.5±2.0</td>
<td>2.8 (−2.0, 7.6)</td>
<td>31.8±2.4</td>
<td>31.2±2.2</td>
<td>−0.9 (−4.8, 3.1)</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDV, mL/m²</td>
<td>216±21</td>
<td>157±25</td>
<td>−58 (−88, −28)$†$</td>
<td>198±25</td>
<td>204±27</td>
<td>6 (−12, 15)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>66±3</td>
<td>56±2</td>
<td>−11 (−16, −5)$†$</td>
<td>68±3</td>
<td>65±2</td>
<td>−3 (−7, 1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>118±4</td>
<td>121±4</td>
<td>3 (−5, 10)</td>
<td>117±4</td>
<td>115±3</td>
<td>−3 (−11, 5)</td>
<td>NS</td>
</tr>
<tr>
<td>QoL</td>
<td>1.5±0.2</td>
<td>1.4±0.2</td>
<td>−0.1 (−0.4, 0.2)</td>
<td>1.5±0.2</td>
<td>1.4±0.2</td>
<td>−0.1 (−1.3, 1.2)</td>
<td>NS</td>
</tr>
<tr>
<td>EuroQoL</td>
<td>68±3.8</td>
<td>64±4.2</td>
<td>−4 (−10, 2)</td>
<td>64±4</td>
<td>62±4</td>
<td>−2 (−10, 6)</td>
<td>NS</td>
</tr>
<tr>
<td>NE, pg/mL</td>
<td>5.89±1.94</td>
<td>4.90±2.51</td>
<td>−0.73 (−2.79, 1.33)</td>
<td>2.67±1.11</td>
<td>2.31±1.04</td>
<td>−0.46 (−1.20, 0.28)</td>
<td>NS</td>
</tr>
<tr>
<td>NT-proBNP, pmol/L</td>
<td>320±62</td>
<td>340±81</td>
<td>38 (−25, 100)</td>
<td>231±56</td>
<td>312±155</td>
<td>55 (−153, 263)</td>
<td>NS</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; QoL, quality of life; and NE, norepinephrine. Data are mean±SEM at baseline and 12 weeks in those patients who completed the study (thalidomide, n=22; placebo, n=26; see Figure 1 for details). Changes are given as mean with 95% CI in parentheses.

*P<0.05, †P<0.01, and ‡P<0.001 vs baseline.

### TABLE 3. Immunologic Parameters at Baseline and After 12 Weeks of Therapy With Thalidomide or Placebo

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 Weeks</th>
<th>Change</th>
<th>Baseline</th>
<th>12 Weeks</th>
<th>Change</th>
<th>Differences in Changes Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α, pg/mL</td>
<td>23±3</td>
<td>30±3</td>
<td>7 (4, 11)$†$</td>
<td>19±2</td>
<td>20±2</td>
<td>1 (−4, 6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>sTNF-RI, pg/mL</td>
<td>1185±105</td>
<td>1217±103</td>
<td>83 (26, 140)$†$</td>
<td>1200±123</td>
<td>1180±135</td>
<td>−20 (61, −93)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TNF-α to sTNF-RI ratio</td>
<td>6.7±0.9</td>
<td>8.3±0.8</td>
<td>1.4 (0.1, 2.8)$*$</td>
<td>5.8±0.8</td>
<td>6.5±1.3</td>
<td>1.0 (−1.3, 3.0)</td>
<td>NS</td>
</tr>
<tr>
<td>IL-10, pg/mL</td>
<td>3.8±0.6</td>
<td>2.5±0.2</td>
<td>−1.4 (−2.4, −0.5)$†$</td>
<td>5.0±1.2</td>
<td>4.2±1.0</td>
<td>−0.3 (−1.2, 0.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IL-8, pg/mL</td>
<td>6±1</td>
<td>12±2</td>
<td>6 (2, 10)$†$</td>
<td>31.0±20</td>
<td>32±21</td>
<td>2 (0, 3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Leukocytes, 10⁹/L</td>
<td>7.3±0.3</td>
<td>6.4±0.3</td>
<td>−0.9 (−1.4, −0.3)$†$</td>
<td>6.9±0.2</td>
<td>6.8±0.3</td>
<td>−0.2 (−0.6, 0.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Neutrophils, 10⁹/L</td>
<td>4.7±0.3</td>
<td>3.4±0.2</td>
<td>−1.2 (−1.7, −0.8)$†$</td>
<td>4.0±0.3</td>
<td>4.1±0.2</td>
<td>0.0 (−0.5, 0.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Monocytes, 10⁹/L</td>
<td>0.62±0.04</td>
<td>0.75±0.04</td>
<td>0.13 (0.04, 0.22)$†$</td>
<td>0.63±0.05</td>
<td>0.58±0.04</td>
<td>−0.05 (−0.12, 0.02)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Eosinophils, 10⁹/L</td>
<td>0.17±0.02</td>
<td>0.40±0.05</td>
<td>0.21 (0.13, 0.29)$†$</td>
<td>0.18±0.02</td>
<td>0.19±0.02</td>
<td>0.00 (−0.03, 0.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphocytes, 10⁹/L</td>
<td>1.76±0.12</td>
<td>1.73±0.13</td>
<td>−0.04 (−0.16, 0.09)</td>
<td>1.92±0.12</td>
<td>1.91±0.13</td>
<td>−0.03 (−0.16, 0.11)</td>
<td>NS</td>
</tr>
<tr>
<td>MMP-2, ng/mL</td>
<td>43±2</td>
<td>37±2</td>
<td>−4 (−6, −2)$*$</td>
<td>34±2</td>
<td>35±2</td>
<td>0 (−2, 2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TIMP-1, ng/mL</td>
<td>79±10</td>
<td>64±9</td>
<td>−7 (−17, 41)</td>
<td>90±13</td>
<td>57±7</td>
<td>−36 (−61, −11)$*$</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are mean±SEM at baseline and 12 weeks in those patients who completed the study (thalidomide, n=22; placebo, n=26; see Figure 1 for details). Changes are given as mean with 95% CI in parentheses. The TNF-α to sTNF-RI value is expressed as a molar ratio.

*P<0.05, †P<0.01, and ‡P<0.001 vs baseline.
Effect of Thalidomide in Relation to Dosage
When the patients were divided into 2 groups according to their achieved thalidomide dosage (ie, <200 mg QD or =200 mg QD; the continuous variable dosage was dichotomized because of small numbers, and in addition, 56% of the patients achieved a thalidomide dosage of 200 mg QD), we found that the increase in LVEF (11.6±3.63 versus 2.5±1.99 EF units, P<0.05) and the decrease in total leukocyte (−1.82±0.35 versus −0.21±0.36 10⁹/L, P<0.01) and neutrophil (−1.52±0.36 versus −0.61±0.18 10⁹/L, P<0.01) counts were significantly more pronounced in those patients who received the highest thalidomide dosage, suggesting a dose-response pattern for these parameters. Moreover, patients with IDCM tended to reach a higher daily thalidomide dosage than those with CAD (179±57 versus 125±67 mg, P=0.087), possibly contributing to the more marked increase in LVEF in the former group (Figure 2).

Side Effects and Laboratory Status
The adverse events are detailed in Table 4. Twenty-five patients (89%) in the thalidomide group and 16 (57%) in the placebo group experienced some adverse event during treatment (P<0.05). As for serious adverse events, there were 2 hospitalizations in both the placebo (1 due to myocardial infarction and 1 due to pneumonia) and the thalidomide (1 due to worsening of CHF and 1 due to syncope) groups. However, the only death occurred in the thalidomide group (sudden death). In contrast to these clinical adverse events, there were no changes in hemoglobin levels, thrombocyte counts, electrolytes, serum creatinine, or liver enzymes in either group, except for a decline in γ-glutamyl transferase, from 47±8 to 27±6 mmol/L (P<0.001) during thalidomide treatment.

Long-Term Follow-Up
After finishing the intervention study (12 weeks), 6 of the patients with the most marked increase in LVEF during thalidomide treatment (>5 EF units, all with IDCM) were followed up for 1 additional year before LVEF and LVEDV were measured again. Notably, after 1 year without thalidomide therapy, LVEF had returned to baseline (23.5±2.2, 37.3±4.0, and 23.8±2.4 EF units), and LVEDV was even higher than at baseline in these 6 IDCM patients (218±27, 143±28, and 277±35 mL/m²)(data represent measurements at baseline; at the end of the study, ie, 12 weeks). Other abbreviations are as defined in text.
1-year follow-up, respectively). However, we cannot conclude that these parameters slowly returned to baseline levels or if they had returned to baseline immediately after discontinuation of therapy.

**Discussion**

In the present double-blind, placebo controlled study, we report that thalidomide increases LVEF and that these changes are accompanied by a decrease in LVEDV, suggesting that thalidomide can alleviate adverse myocardial remodeling and improve LV function in CHF. Importantly, this improvement in LV function occurred in patients who were clinically stable and who, in the majority of cases, were receiving angiotensin-converting enzyme inhibitors or angiotensin II and β-blockers in addition to diuretics. These findings may suggest a role for thalidomide in the management of CHF in addition to traditional cardiovascular medications.

It is well known that angiotensin-converting enzyme inhibitors and β-blockers have a favorable effect on LV remodeling that is associated with improved survival.22 In addition to EF, LV volume has been shown to be an important predictor of survival in CHF and after myocardial infarction,23,24 and a relation between attenuation of remodeling and clinical benefit has been observed in CHF patients.25 The beneficial effect of thalidomide on LV remodeling, as assessed by the increased LVEF and decreased LVEDV, may therefore be clinically important. Interestingly, despite treatment with β-blockers in most patients, thalidomide reduced HR, and such an effect has also previously been reported in multiple myeloma patients receiving this medication.26 Because selective HR reduction improves contractility and reduces ischemia,27 this reduction in HR might contribute to the beneficial effect of thalidomide on LV function, possibly involving enhanced diastolic perfusion time and decreased myocardial oxygen demand.

Recently, thalidomide has generated renewed interest because of its immunomodulatory properties.6,7 Herein we show that improvement in LV function during thalidomide therapy was accompanied by a significant decrease in total leukocyte and neutrophil counts, further supporting the concept of immunomodulatory effects for this medication. Several reports suggest a pathogenic role for neutrophil infiltration in myocardial reperfusion injury.27,28 Recently, these cells have also been implicated in the pathogenesis of CHF, possibly related to their ability to stimulate an inappropriate production of nitric oxide.29 Previous reports have shown that thalidomide attenuates neutrophil activation,30 and one might hypothesize that the downregulatory effect of thalidomide on neutrophils contributes to its beneficial effects in CHF.

Until now, thalidomide has been regarded as an anti-TNF drug, primarily because of evidence presented in vitro studies and in animal models.31 However, studies analyzing the effect of thalidomide on plasma levels of TNF-α in human have shown discrepant results, demonstrating suppressive,12,14 no,15,32 or even enhancing14 effects. Most of these studies have been small pilot trials without any placebo group. However, in the present double-blind, placebo controlled study, we have shown that thalidomide increases plasma levels of TNF-α and the TNFα–sTNF-RI ratio in CHF; notably, one of the few previous placebo-controlled studies in humans that analyzed the effect of thalidomide on plasma levels of TNF-α reported similar findings.33 Although we have no data on interference with heterophile antibodies in the actual TNF-α EIA, we have previously shown a good correlation between TNF-α immunoreactivity and bioactivity with this particular EIA.19 Moreover, we have recently shown increased gene expression of TNF-α in freshly isolated peripheral blood mononuclear cells from CHF patients receiving thalidomide, and such an upregulation was also seen within the myocardium when we analyzed the effect of thalidomide in a rat model of CHF (authors’ unpublished data, 2005), suggesting that this increase in TNF-α levels during thalidomide treatment is real. Thus, although the effect of thalidomide on TNF-α potentially differs among different cell types,6,7 our results clearly challenge the view of thalidomide as an anti-TNF drug.

We and others have suggested a role for inflammation and TNF-α, in particular, in the pathogenesis of CHF,3–5 and the present study, showing improved LV function accompanied by an increase in plasma levels of TNF-α and IL-8, may seem to conflict with such previous hypotheses. This may not be the case, however. Thus, the improvement in LVEF may not necessarily have occurred because of but rather in spite of the changes in TNF-α levels. In fact, although thalidomide may enhance the levels of certain inflammatory cytokines, other immunomodulatory effects of this same medication, such as downregulation of neutrophils, could counteract it. Moreover, the beneficial effect of thalidomide in CHF may not be directly related to its effects on cytokines but could involve other mechanisms, such as effects on matrix degradation, as well as direct effects on the myocardium. In fact, we demonstrated downregulatory effects of thalidomide on MMP-2 accompanied by no changes in MMP-1 levels, suggesting an attenuated MMP activity during thalidomide therapy. Recent evidence implicates the MMP family as potential mediators in the pathogenesis of CHF by promoting cardiac remodeling and dilation,70,21 and we hypothesize that the downregulatory effect of thalidomide on the MMP-TIMP balance could be important in the beneficial effect of thalidomide on cardiac remodeling. Thus, rather than an antiinflammatory agent, we suggest that thalidomide has a potential as a matrix-stabilizing agent, leading to attenuated myocardial remodeling, and notably, such downregulatory effects of thalidomide on MMP have also been reported by others.15

In the present study, we found that the effect of thalidomide on LVEF at least partly was dependent on the etiology of CHF. Thus, although there was a marked increase in LVEF in IDC, the increase noted in CAD was more moderate. Moreover, all dropouts during thalidomide therapy were in the CAD group, suggesting some difference in toxicity between CAD and IDC. The reasons for these findings are at present unclear, but we cannot exclude the possibility that thalidomide acts differently in these 2 subgroups of CHF. However, the IDC patients also achieved a higher mean thalidomide dosage, possibly contributing to the different LVEF response between IDC and CAD, and these issues will need to be further clarified in larger forthcoming studies.

Although the present study suggests a role for thalidomide in the management of CHF, a small number of patients, especially those with IDC, were studied. Moreover, the study period was relatively short (ie, 12 weeks), and because the effect on LVEF is usually time dependent,34 we cannot exclude different effect...
outcomes of thalidomide therapy during long-term follow-up. Moreover, the lack of data on ventricular function between baseline and the end of the study as well as the relatively large numbers of dropouts in the thalidomide group represent limitations of the present study. Furthermore, the relatively high number of side effects in the thalidomide group, even if the dosages were relatively low compared with those that have been used in the treatment of cancer patients, underscores the need for more accurate evaluation of the safety profile of thalidomide in CHF. These preliminary observations should therefore clearly be confirmed in a larger prospective study with morbidity and mortality as end points. Such studies should also more precisely try to define the optimal dosage as well as the mechanisms of action of this medication.

Acknowledgments

We thank Penn Pharmaceutical, London, UK, for providing the thalidomide capsules. We thank the Norwegian Research Council for financial support.

Disclosure

Dr Semb has received an independent grant from Bristol-Myers Squibb for research and advisory board honoraria from AstraZeneca, Schering Plough, and Merck Sharp & Dohme.

References

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_Circulation._ 2005;112:3408-3414; originally published online November 21, 2005; doi: 10.1161/CIRCULATIONAHA.105.564971
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/112/22/3408

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