Double-Blind, Randomized Trial of an Anti-CD18 Antibody in Conjunction With Recombinant Tissue Plasminogen Activator for Acute Myocardial Infarction

Limitation of Myocardial Infarction Following Thrombolysis in Acute Myocardial Infarction (LIMIT AMI) Study

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Background—Inhibition of leukocyte adhesion can reduce myocardial infarct size in animals. This study was designed to define the safety and efficacy of a recombinant, humanized, monoclonal antibody to the CD18 subunit of the β2 integrin adhesion receptors (rhuMAb CD18), in reducing infarct size in patients treated with a thrombolytic agent.

Methods and Results—The Limitation of Myocardial Infarction following Thrombolysis in Acute Myocardial Infarction Study (LIMIT AMI) was a randomized, double-blind, placebo-controlled, multicenter study conducted in 60 centers in the United States and Canada. A total of 394 subjects who presented within 12 hours of symptom onset with ECG findings (ST-segment elevation) consistent with AMI were treated with recombinant tissue plasminogen activator and were also given an intravenous bolus of 0.5 or 2.0 mg/kg rhuMAb CD18 or placebo. Coronary angiography was performed at 90 minutes, 12-lead ECGs were obtained at baseline, 90, and 180 minutes, and resting sestamibi scans were performed at ±120 hours. Adjunctive angioplasty and use of glycoprotein IIb/IIIa antiplatelet agents at the time of angiography were discretionary. There were no treatment effects on coronary blood flow, infarct size, or the rate of ECG ST-segment elevation resolution, despite the expected induction of peripheral leukocytosis. A slight trend toward an increase in bacterial infections was observed with rhuMAb CD18 (P=0.33).

Conclusions—RhuMAb CD18 was well tolerated but not effective in modifying cardiac end points. (Circulation. 2001; 104:2778-2783.)

Key Words: myocardial infarction ■ cell adhesion molecules ■ inflammation ■ antibodies ■ trials

Inhibition of leukocyte adhesion with antibodies to the β2 family of leukocyte adhesion molecules (CD18/CD11 dimers) reduced ischemia-reperfusion injury after acute myocardial infarction (AMI) associated with inflammation in animals.1–6 AMI in patients is often associated with inflammation, which is indicative of a poor outcome.7,8 The present study was designed to evaluate the safety and efficacy of a recombinant, humanized, monoclonal antibody to the CD18 subunit of β2 integrin adhesion receptors (rhuMAb CD18), in patients with AMI treated by thrombolysis.

Methods

The Limitation of Myocardial Injury following Thrombolysis in Acute Myocardial Infarction (LIMIT AMI) study was a randomized, double-blind, placebo-controlled, multicenter, 3-group study conducted in 60 centers in the United States and Canada between September 1998 and March 2000. It was approved by Institutional Review Boards at each institution. All subjects provided written, informed consent.

Patients

Subjects with symptoms and ECG findings consistent with AMI (chest pain >30 minutes duration with ST-segment elevation
The primary end point was the corrected TIMI frame count (CTFC) at 90 minutes. Secondary efficacy end points were percent TIMI grade 3 flow at 90-minute angiography, myocardial infarct size assessed by SPECT at ≥120 hours, and ECG ST-segment elevation resolution at 3 hours. In addition, TIMI myocardial perfusion grade during angiography and ECG ST-segment resolution immediately before angiography were assessed. Prospective calculations for selection of sample size were based on 80% power for observing a 15% difference in the proportion of subjects with TIMI 3 flow, ie, 55% (placebo) versus 70% (rhuMAb CD18).

### Coronary Blood Flow

Angiograms were performed conventionally, and end points were determined by the blinded investigator (C.M.G.), who recorded CTFC, TIMI flow grade, and perfusion grade within a window of 80 to 120 minutes after the administration of rtPA (85% of patients). In a few cases, missing CTFC data were imputed as the median CTFC of TIMI flow grade. End point values for completely missing data (death or cardiogenic shock before 105 minutes) were imputed as 100 for CTFC and 0 for TIMI flow grade.

### Infarct Size

Infarct size was assessed by 99mTc-sestamibi SPECT imaging at rest or ≥120 hours after drug administration. The proportion of the left ventricle perfusion deficit was estimated conventionally.12 Missing data (missing or ≤120 hours) were imputed by linear regression from creatine kinase-MB 72-hour time-activity curves.13,14 If creatine kinase-MB data were incomplete (early death), the 90th percentile of SPECT-determined infarct size was imputed.

### ECG ST Segment Elevation Resolution

Standard 12-lead ECGs were obtained at baseline and at 90 and 180 minutes after rtPA. When possible, the 90-minute ECG was obtained before angiography. ECGs were analyzed by a blinded core laboratory that characterized ST-segment elevation 20 ms after the J point. The percentage resolution from baseline in the sum of ST elevation was categorized as follows: complete (≥70%), partial (30% to <70%), or absent (0 to <30%).15 In 60 to 120 minute (90-minute) and 120 to 240 minute (3-hour) windows.

### Statistical Analysis

Continuous variable results are expressed as mean±SD, medians, and percentiles. Two comparisons were prospectively defined for efficacy end points: placebo versus low dose and placebo versus high

### Table 1. Baseline Characteristics and Selected Concomitant Medications

<table>
<thead>
<tr>
<th>Age, y</th>
<th>58.3 (n=134)</th>
<th>58.5 (n=129)</th>
<th>59.6 (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, %</td>
<td>67</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>16</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Anterior MI, %</td>
<td>47</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>Time from onset of MI symptoms to rtPA, hr</td>
<td>3.6 (2.9)</td>
<td>3.3 (2.7)</td>
<td>3.4 (2.6)</td>
</tr>
</tbody>
</table>

Values are mean (median) or percent. BMI indicates body mass index; MI, myocardial infarction; and PTCA, percutaneous transluminal coronary angioplasty.

≥1 mm in ≥2 contiguous leads on a 12-lead ECG who were eligible for treatment with front-loaded recombinant tissue plasminogen activator (rtPA) were included. Exclusion criteria were symptom duration >12 hours; oral temperature ≥101.5°F; treatment with any thrombolytic agent within 4 days; previous coronary surgery; cardiogenic shock (systolic blood pressure <90 mm Hg with intravenous vasopressors or <80 mm Hg without intravenous vasopressors); inability to undergo cardiac catheterization, including known contrast dye allergy; major surgery, biopsy of a parenchymal organ, or significant trauma, within 3 months; prolonged cardiopulmonary resuscitation (>2 minutes) within 2 weeks; recent noncompressible vascular puncture; left bundle branch block; systolic blood pressure >180 mm Hg and/or diastolic blood pressure >110 mm Hg on ≥1 reliable measurement during admission; bleeding disorder within the past 6 months; any history of stroke, transient ischemic attack, or central nervous system structural damage; therapeutic oral anticoagulation (defined as an international normalized ratio [INR] ≥1.4); pregnancy; parturition within 30 days; childbearing potential not using adequate birth control methods; active infection or current use of oral antibiotics; other serious illness (eg, active cancer, HIV infection); other illnesses or therapies known to impair the immune system, such as nontopical corticosteroids; inability to follow the protocol and comply with follow-up requirements; current participation in another experimental drug or device treatment protocol; prior administration of rhuMAb CD18; or any other condition that the Investigator believed would pose a significant hazard to the subject if the investigational therapy were administered.

### Treatment Regimen

Subjects were randomized by a dynamic Interactive Voice Response System, in a 1:1:1 ratio, to 0.5 mg/kg or 2.0 mg/kg rhuMAb CD18 or to matching placebo administered before commencing rtPA or as soon as possible thereafter plus aspirin (325 mg) and intravenous heparin (4000 to 5000 U bolus, followed by 800 to 1000 U/h initially). The target activated partial thromboplastin time for heparinization was 55 to 80 seconds. Coronary angiography was performed 90 minutes after rtPA administration. After obtaining a view of the infarct-related artery, intervention with balloon angioplasty and/or coronary stent placement was performed at the investigator’s discretion after 90 minutes, unless clinically mandated earlier. The duration of heparinization and the use of other medications, such as glycoprotein IIb/IIIa inhibitors, were at the attending physician’s discretion.

### End Points

The primary end point was the corrected TIMI frame count (CTFC) at 90 minutes. Secondary efficacy end points were percent TIMI grade 3 flow at 90-minute angiography, myocardial infarct size assessed by SPECT at ≥120 hours, and ECG ST-segment elevation resolution at 3 hours. In addition, TIMI myocardial perfusion grade during angiography and ECG ST-segment resolution immediately before angiography were assessed. Prospective calculations for selection of sample size were based on 80% power for observing a 15% difference in the proportion of subjects with TIMI 3 flow, ie, 55% (placebo) versus 70% (rhuMAb CD18).
dose. The Wilcoxon rank sum test was used to compare CTFC. Infarct size comparisons were performed using the Cochran-Mantel-Haenszel test, with rank scores stratified by infarct location. The test was used to compare the other efficacy end points. Significance was defined as $P \leq 0.05$.

**Results**

A total of 394 subjects were randomized and treated with rhuMAb CD18 or placebo. An additional 22 subjects were withdrawn before study drug administration. Patient characteristics are shown in Table 1.

There were no differences between placebo and active rhuMAb CD18 groups in any efficacy end point (Figure 1 and Table 2). The incidence of TIMI grade 3 flow in the placebo group was unexpectedly high (66%). Neither the proportion of subjects with TIMI myocardial perfusion grade 2 or 3 or infarct size or ECG ST-segment resolution end points exhibited a treatment effect (Table 3). No treatment effect was observed in the following subgroups (data not shown): treatment $\leq$ 3 hours, men versus women, or use of a glycoprotein IIb/IIIa inhibitor in the first 2 days.

There was no excess of any specific adverse event in the rhuMAb CD18 groups. However, when adverse event terms were grouped as those consistent with a "likely bacterial infection" (defined as sepsis, nonaspiration pneumonia, urinary tract infection, pyuria, abscess, furunculosis, nonviral infection, and abnormal healing) a trend toward a conse-

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**Discussion**

Our results demonstrated no effects of rhuMAb CD18 on multiple cardiac end points. The failure of anti-CD18 therapy in human subjects, despite positive findings in most experimental animal studies,1,2,4,16 was surprising. However, results in canine models were varied, with no effect on infarct size, despite an apparent increase in post-reperfusion blood flow in one study6 and efficacy in another with 2 of 3 anti-CD18 antibodies tested. In a third study, efficacy was not seen when myocardial ischemia was severe.17

One possible explanation for the failure of anti-CD18 therapy in humans is that the duration of ischemia is so long that endothelial cell barrier function fails. If so, blocking the Mac-1–intracellular adhesion molecule interaction would not prevent neutrophils from migrating into the subendothelial tissues and contributing to tissue damage. The median time of presentation (2.7 hours) was longer than the $\leq$ 90 minutes of experimental ischemia studied in animals. In rabbits with myocardial infarction, anti-CD18 therapy was effective after

**TABLE 2.** CTFC, TIMI Flow Grade, and TIMI Myocardial Perfusion Grade 90 Minutes After the Administration of rtPA and Study Drug*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>RhuMAb CD18 0.5 mg/kg</th>
<th>RhuMAb CD18 2.0 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n†</td>
<td>114</td>
<td>111</td>
<td>108</td>
</tr>
<tr>
<td>CTFC, frames</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>46±31</td>
<td>51±32</td>
<td>45±29</td>
</tr>
<tr>
<td>CTFC, frames, median</td>
<td>33</td>
<td>38</td>
<td>35</td>
</tr>
<tr>
<td>TIMI grade 3 flow, %</td>
<td>66</td>
<td>58</td>
<td>63</td>
</tr>
<tr>
<td>TIMI grade 2 flow, %</td>
<td>15</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>TIMI grade 0/1 flow, %</td>
<td>19</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>n†</td>
<td>107</td>
<td>101</td>
<td>102</td>
</tr>
<tr>
<td>TIMI myocardial perfusion grade 2 or 3, %</td>
<td>48</td>
<td>55</td>
<td>49</td>
</tr>
<tr>
<td>TIMI myocardial perfusion grade 0 or 1, %</td>
<td>52</td>
<td>45</td>
<td>51</td>
</tr>
</tbody>
</table>

*No statistically significant comparisons.
†Number of evaluable subjects within the time window of 80 to 105 minutes from rtPA administration.

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**Figure 1.** Primary end point: corrected TIMI frame count 90 minutes after rtPA administration.
coronary occlusion lasting 30 but not 45 minutes. By contrast, in dogs with neutrophil depletion, myocardial necrosis was reduced with ischemia of either 90 or 240 minutes. Sharar et al found, using a rabbit ear preparation and 6 hours of occlusion, that administration of anti-CD18 therapy immediately on reperfusion was as effective as that initiated 1 hour but not 4 hours later. No effect was observed when the antibody was administered after 12 hours.

At least 2 in vitro studies have reported CD18-independent migration across human endothelial cell layers in response to selected stimuli. The mechanism of CD18-independent migration is not understood. It may be organ-dependent, with blocking antibodies consistently showing complete inhibition of neutrophil migration into skin but not into lung or liver. Although other families of adhesion receptors are well known, it is the β2 family, all of which contain CD18 subunits, that is thought to enable firm neutrophil attachment as a prelude to migration. Leukocytes and/or acute inflammation may not be critical to the amount of myocardial damage after coronary occlusion in humans. This possibility is consistent with the failure of large doses of methylprednisolone to improve AMI outcome.

Medications with possible activity against leukocyte adhesion used in this study included unfractionated heparin and abciximab. Either could have influenced the effects of rhuMAb CD18. Doses of unfractionated heparin low enough not to affect the activated partial thromboplastin time bind to Mac-1 and interfere with n-formyl-methionine-leucine-phenylalanine (fMLP)-induced leukocyte-endothelial adhesion in rats. The time course of the leukocytosis after anti-CD18 therapy is consistent with the prevention of margination of leukocytes, and yet this anti-adhesion phenomenon has not been reported with either heparin or abciximab. Mac-1 (CD18/11b, occurring mainly on neutrophils and monocytes) is also a receptor for C3bi and fibrinogen. Interference with its functions is seen in vivo and in vitro at clinically relevant concentrations of heparin. Thus, heparin may have interfered with anti-CD18 effects in this study.

Despite an unexpectedly high proportion of subjects with TIMI grade 3 flow at 90 minutes after rtPA (66%) in the placebo group, the study had adequate power to detect treatment effects. The power of this study to demonstrate the expected 15% absolute increase in TIMI grade 3 flow rate (from the observed rate of 66% to 81%) was 70%. The protocol design was sufficiently sensitive to detect clinically relevant effects of anti-CD18 treatment in view of the multiple cardiac end points assessed. Coronary flow and 90-minute ECG end points were obtained before mechanical intervention to avoid confounding effects of the intervention itself. Blinded core reference laboratories were used to assess efficacy end points independently. The levels of missing data were acceptable, and the findings were robust in regard to analysis methods. The doses studied resulted in the expected plasma concentrations and were sufficient to fully saturate CD18 receptors within the first few hours. Biological activity was evident, as judged from the 2-fold rise in mean peripheral white cell counts in both active treatment groups. Thus, it seems that dosage was adequate.

Our results indicate that rhuMAb CD18 was well tolerated but lacked any beneficial cardiac effects in patients with ST-segment elevation AMI.

### TABLE 3. Myocardial Infarct Size and ECG ST-Segment Resolution*

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>RhuMAb CD18 0.5 mg/kg</th>
<th>RhuMAb CD18 2.0 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>133</td>
<td>129</td>
<td>129</td>
</tr>
<tr>
<td>Myocardial infarct size (SPECT), median % left ventricular defect size</td>
<td>10</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>n†</td>
<td>133</td>
<td>129</td>
<td>129</td>
</tr>
<tr>
<td>Myocardial infarct size (CK-MB, gram equivalents), median units</td>
<td>13</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>n†</td>
<td>109</td>
<td>103</td>
<td>106</td>
</tr>
<tr>
<td>ECG ST-segment elevation resolution ≥70% at 180 minutes, %</td>
<td>61</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>n†</td>
<td>91</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>ECG ST-segment elevation resolution ≥70% at 90 minutes, %</td>
<td>42</td>
<td>34</td>
<td>41</td>
</tr>
</tbody>
</table>

*No statistically significant comparisons.
†Number of subjects evaluable within time window from treatment (see Methods for specifications).

CK indicates creatine kinase.

**Figure 2.** Time course of mean peripheral white blood cell (WBC) counts by treatment.
### TABLE 4. Safety Outcomes*

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=134)</th>
<th>RhuMAb CD18 0.5 mg/kg (n=129)</th>
<th>RhuMAb CD18 2.0 mg/kg (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, †%</td>
<td>6</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>All serious adverse events, † n</td>
<td>30</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>All infections, † %</td>
<td>37</td>
<td>40</td>
<td>34</td>
</tr>
<tr>
<td>Likely bacterial infection, †%</td>
<td>11</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>All bleeding events, † %</td>
<td>59</td>
<td>64</td>
<td>67</td>
</tr>
<tr>
<td>Serious and life-threatening bleeding, † %</td>
<td>6</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Recurrent myocardial infarction, †%</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Coronary bypass surgery, † %</td>
<td>13</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Serious/severe heart failure, †§</td>
<td>7</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Composite end point of death, recurrent AMI, or serious/severe heart failure, † %</td>
<td>12</td>
<td>11</td>
<td>15</td>
</tr>
</tbody>
</table>

*No statistically significant comparisons.
†Up to and including day 30.
§Up to the first hospital discharge.
†§Defined as reports of heart failure of Killip class III or IV, readmission for heart failure, or serious or severe adverse events of heart failure.

### Data Safety Monitoring Board

Chairperson: P. Armstrong; Members: S. Emerson, C. Grines, J.W. Kennedy

### Central Laboratories


### Clinical Centers in Order of Enrollment

**United States (356 Patients)**

John Nasseff Heart Hospital, St Paul, Minn; Project Investigator, K. Baran; Research Coordinators, C. Iacarella and B. Bruhn-Ding. Rhode Island Hospital, Providence, RI; Project Investigator, G.R. McKendall; Research Coordinator, M. Grogan. Maine Medical Center, Portland, Maine; Project Investigator, C.T. Lambrew; Research Coordinator, S. Bosworth-Farrell. Jane Phillips Medical Center, Brooklyn, NY: Project Investigator, J. Shani; Research Coordinator, M. Silver; Research Coordinator, J. Christopher. Parkview Memorial Hospital, Fort Wayne, Ind; Project Investigator, S. Brown; Research Coordinator, J. Fisher. Sharp Memorial Hospital, San Diego, Calif; Project Investigator, J.B. Gordon; Research Coordinator, P. Bakkum. University of Alabama Medical Center, Birmingham: Project Investigator, W.J. Rogers. Maimonides Medical Center, Brooklyn, NY: Project Investigator, J. Shani; Research Coordinator, K. Brett. Winona Hospital, Indianapolis, Ind; Project Investigator, J. 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Acknowledgments

The study was sponsored by Genentech, Inc, South San Francisco, California.

References


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for the LIMIT AMI Investigators

Circulation. 2001;104:2778-2783
doi: 10.1161/hc4801.100236

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

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