Pexelizumab, an Anti-C5 Complement Antibody, as Adjunctive Therapy to Primary Percutaneous Coronary Intervention in Acute Myocardial Infarction

The COMplement inhibition in Myocardial infarction treated with Angioplasty (COMMA) Trial

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Background—Complement, activated during myocardial ischemia and reperfusion, causes myocardial damage through multiple processes. The COMplement inhibition in Myocardial infarction treated with Angioplasty (COMMA) trial was performed to determine the effect of pexelizumab, a C5 complement inhibitor, on infarct size in patients with ST-segment–elevation myocardial infarction (MI) undergoing primary percutaneous coronary intervention.

Methods and Results—In COMMA, 960 patients with MI (20% isolated inferior MI) were randomized to placebo, pexelizumab 2.0-mg/kg bolus, or pexelizumab 2.0-mg/kg bolus and 0.05-mg/kg per h infusion for 20 hours. Infarct size by creatine kinase–MB area under the curve, the primary outcome, did not differ significantly between groups (placebo median, 4393; bolus pexelizumab, 4526; bolus plus infusion pexelizumab, 4713 [ng/mL] · h; \( P = 0.89 \) for bolus versus placebo; \( P = 0.76 \) for bolus plus infusion versus placebo), nor did the composite of 90-day death, new or worsening heart failure, shock, or stroke (placebo, 11.1%; bolus, 10.7%; bolus plus infusion, 8.5%). The ninety-day mortality rate was significantly lower with pexelizumab bolus plus infusion (1.8% versus 5.9% with placebo; nominal \( P = 0.014 \)); the bolus-only group had an intermediate mortality rate (4.2%).

Conclusions—In patients with ST-elevation MI undergoing percutaneous coronary intervention, pexelizumab had no measurable effect on infarct size. However, the significant reduction in mortality suggests that pexelizumab may benefit patients through alternative novel mechanisms and provides impetus for additional investigation. (Circulation. 2003; 108:1184-1190.)

Key Words: myocardial infarction ■ angioplasty ■ inflammation ■ reperfusion

Complement activation in acute myocardial infarction (MI) is an important mediator of inflammatory damage and is associated with larger infarctions and poor clinical outcomes. The accumulation of terminal complement complex in the ischemic myocardium early during reperfusion suggests its involvement in reperfusion myocardial damage.

The Complement And ReDuction of INfarct size after Angioplasty or Lytics (CARDINAL) program included 2 phase II trials testing whether pexelizumab, a monoclonal antibody against C5 complement, reduces infarct size or improves clinical outcomes when used with reperfusion therapy. In the COMplement inhibition in myocardial infarction treated with thromboLYtics (COMPLY) trial, neither infarct size nor clinical outcomes were improved with pexelizumab (see p 1176 of this issue).

Compared with fibrinolysis, however, primary percutaneous coronary intervention (PCI) produces a different pattern of reperfusion, including abrupt distal embolization, that may present a different target for anticomplement therapy. Animal studies, in which complement inhibition reduced inflammatory damage, apoptosis, and infarct size, used coronary
ligation and release, perhaps more closely mimicking PCI versus thrombolysis.

We report results of the second CARDINAL study, COMplement inhibition in Myocardial infarction treated with Angioplasty (COMMA). Its primary objective was to determine whether adjunctive pexelizumab with primary PCI reduces infarct size determined by creatine kinase (CK)-MB area under the curve (AUC) through 72 hours. Secondary end points included a 90-day composite clinical outcome (death, new or worsening congestive heart failure [CHF], cardiogenic shock, or stroke) and the individual components of the composite. Other end points included safety and tolerability.

Methods

Patients

Patients ≥18 years of age were eligible if they arrived <6 hours after symptom onset with ST-segment elevation ≥2 mm in 2 contiguous leads or new left bundle-branch block. Exclusion criteria included previous abnormal hematologic function (hemoglobin <9.5 g/dL, white blood cell count <3000/mm³, neutrophil count <1200/mm³, or platelet count <100 000/mm³), known or suspected active neisserial infection, known or suspected hereditary complement deficiency, prior renal impairment (serum creatinine >3.0 mg/dL), or evidence of serious active infection. The decision to treat patients with primary PCI must have been made before recruitment. Informed consent was required for participation, and institutional review boards at all hospitals approved the protocol.

Recruitment

Enrollment continued from January 2000 to April 2002. Eligible patients were randomly assigned to treatment and stratified within each site and by infarct location. Enrollment of patients with ST-segment elevation only in the inferior leads was capped at 20% to ensure a higher-risk population.

Treatment and Follow-Up

Patients were randomly assigned to receive (1) placebo bolus and placebo infusion; (2) 2.0-mg/kg bolus of pexelizumab and placebo infusion for 20 hours; or (3) 2.0-mg/kg bolus and 0.05-mg/kg per h infusion of pexelizumab for 20 hours. The bolus was to be given before first balloon inflation, and infusions were started 4 hours after the bolus. All additional therapies were at the discretion of attending physicians.

Patients were followed for in-hospital adverse events and clinical end points. Patients were seen at 14, 30, and 90 days and contacted at 6 months to determine survival status.

Infarct Size Assessment

CK and CK-MB were measured at enrollment (baseline) and at 4, 8, 12, 16, 24, 36, 48, and 72 hours after enrollment. Infarct size by CK-MB AUC was calculated by using the linear-trapezoidal method from data available through 72 hours. Imputation and interpolation techniques were similar to those used in COMPLY.

Clinical End Points

The definitions of CHF, cardiogenic shock, and stroke were the same as in COMPLY.

Pharmacodynamic and Human Anti-Human Antibody Assays

Blood samples for pharmacodynamic assessment of complement suppression (hemolytic activity) were drawn at enrollment and at 4, 12, 24, 36, 48, and 72 hours after bolus dosing. Assays for IgG and IgM human anti-human antibodies (HAHA) were performed at enrollment (baseline) and at 14, 30, and 90 days. Increases from baseline of 4-fold or greater were considered positive.

Results

In all, 960 patients were enrolled (Figure 1). Baseline characteristics were similar between groups (Table 1), although patients in the bolus-plus-infusion group had somewhat greater baseline cardiac biomarker and ST-segment elevations. Study drug began a median 15 to 17 minutes before first balloon inflation (Table 2). Concomitant medication use was comparable between groups (Table 2). More than 90% of patients received platelet glycoprotein IIb/IIIa inhibitors, and 90% underwent coronary stenting.

The median number of CK-MB samples for survivors to 72 hours was similar between groups (8 [interquartile range, 8 to 9] placebo; 9 [8 to 9] bolus; and 9 [8 to 9] bolus plus infusion). The numbers of deaths within 72 hours, and therefore the number of patients requiring imputation of infarct size, were 7, 4, and 5, respectively.

Bolus pexelizumab dosing completely inhibited complement for 4 hours, returning toward baseline by 24 hours, whereas bolus-plus-infusion dosing blocked complement ac-
tivity for 24 hours, with activity returning toward baseline by 36 hours (Figure 2). A positive HAHA titer (IgG and IgM) was rare (in 0 of 156 and 0 of 154 placebo, 0 of 156 and 2 of 153 bolus, and 1 of 153 and 10 of 151 bolus-plus-infusion patients at 14 days and in 0 of 207 and 0 of 204 placebo, 2 of 218 and 0 of 213 bolus, and 0 of 220 and 2 of 218 bolus-plus-infusion patients at 90 days).

Infarct Size
Median infarct size (CK-MB AUC, \(\text{ng/mL} \cdot \text{h}\)) was not significantly different comparing placebo (4393) with bolus of pexelizumab (4526, \(P=0.89\)) or with bolus plus infusion of pexelizumab (4713, \(P=0.76\)) (Figure 3). Median peak CK-MB (ng/mL) also was similar between groups: 212 placebo, 230 bolus, and 229 bolus plus infusion.

Clinical End Points
The 90-day composite of death, new or worsening heart failure, shock, and disabling stroke occurred in 8.5% of the bolus-plus-infusion patients versus 11.1% of the placebo group (relative risk [RR], 0.77; 95% CI, 0.46 to 1.29) (Table 3). A statistically significant 70% relative (4.1% absolute) reduction in 90-day mortality was observed in the bolus-plus-infusion group compared with the placebo group (RR, 0.30; 95% CI, 0.11 to 0.81; \(P=0.014\)), and mortality was intermediate in the bolus-alone group. The cause of death was predominantly cardiovascular, with 2 noncardiovascular deaths in the placebo group and 1 such death in each pexelizumab group. The mortality reduction with bolus-plus-infusion treatment appeared early (1.9% absolute, 52% relative reduction by day 6), became larger over time, and persisted at 6 months (RR, 0.43; 95% CI, 0.20 to 0.94; \(P=0.035\)) (Figure 4). The proportions of patients with complete ST-segment resolution and QRS score results were similar between groups (Table 4).

Adverse Effects
Pexelizumab was well tolerated, and adverse events were not increased. Serious infection occurred in 9 placebo patients, 10 bolus-only patients, and 8 bolus-plus-infusion patients. Sepsis was infrequent (2 placebo patients, 4 bolus patients, and 4 bolus-plus-infusion patients). Myocardial rupture occurred in <1% of patients (1 placebo, 1 bolus, and 1 bolus-plus-infusion).

Discussion
Complement inhibition with pexelizumab used as an adjunct to PCI for ST-segment–elevation MI had no effect on the primary end point of infarct size assessed by CK-MB AUC. Mortality at

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics</th>
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<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Female sex</td>
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<tr>
<td>White race</td>
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<tr>
<td>Weight, kg</td>
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<tr>
<td>Heart rate, per min</td>
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<td>Blood pressure, mm Hg</td>
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<td>Systolic</td>
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<tr>
<td>Diastolic</td>
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<td>III</td>
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<tr>
<td>IV</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Prior cerebrovascular disease</td>
</tr>
<tr>
<td>Prior infarction</td>
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<tr>
<td>Prior heart failure</td>
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<tr>
<td>Smoking status</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Current</td>
</tr>
<tr>
<td>CK-MB, ng/mL</td>
</tr>
<tr>
<td>Troponin I, ng/mL</td>
</tr>
<tr>
<td>Sum ST-segment elevation, mm</td>
</tr>
</tbody>
</table>

Data are medians (interquartile range) or percentages.
90 days was significantly reduced, however, with an absolute difference of 4.1% and a relative risk reduction of 70%.

The reduced mortality rate with no parallel effect on infarct size is an important, unexpected finding. Although the total number of deaths was small and the mortality reduction could be due to chance, several factors support the likelihood of a true treatment effect. Patients who received only bolus dosing had intermediate mortality, consistent with dose-dependent effects. Moreover, the survival benefit in the bolus-plus-infusion group was distributed equally between the early (week 1) and later (week 1 to 90 days) periods. Bolus dosing provided the same early benefit but no later benefit. The bolus-plus-infusion group also had a nonsignificant, 45% lower rate of cardiogenic shock.

How can pexelizumab reduce mortality without reducing infarct size? First, CK-MB AUC may not be precise enough to detect small but clinically relevant treatment effects, and thus a reduction in infarct size was undetected. This seems unlikely, however, given the similar QRS scores at discharge among groups. More likely, effects are independent of early infarct size and mediated through complement effects on longer-term determinants of infarct recovery, such as inflammatory cytokines, apoptosis, inducible nitric oxide synthase, and remodeling.

Inflammation contributes to cell damage during ischemia and reperfusion and decompensation in cardiogenic shock, and markers of inflammation are used prognostically for patients with acute coronary syndromes. The complement system is a central mediator of inflammation, and terminal components of the complement cascade include the most potent anaphylatoxin (C5a) and the membrane attack complex (C5b-9) that causes direct cytotoxicity, generation of

Table 2. Treatment Details

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=271)</th>
<th>Bolus (n=262)</th>
<th>Bolus + Infusion (n=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom onset to enrollment, h</td>
<td>2.4 (1.65 to 3.7)</td>
<td>2.3 (1.7 to 3.3)</td>
<td>2.45 (1.8 to 2.5)</td>
</tr>
<tr>
<td>Symptom onset to balloon inflation, h</td>
<td>3.25 (2.2 to 4.6)</td>
<td>3.05 (2.3 to 4.1)</td>
<td>3.3 (2.5 to 4.4)</td>
</tr>
<tr>
<td>Study drug to PCI start, min</td>
<td>17 (12 to 26)</td>
<td>16 (10 to 25)</td>
<td>15 (11 to 26)</td>
</tr>
<tr>
<td>Hours of study-drug infusion</td>
<td>20.0 (20.0 to 20.0)</td>
<td>20.0 (20.0 to 20.0)</td>
<td>20.0 (20.0 to 20.0)</td>
</tr>
</tbody>
</table>

Aspirin | 95 | 98 | 93 |
β-Blocker | 97 | 95 | 99 |
ACE inhibitor | 83 | 83 | 86 |
Nitroglycerin | 84 | 82 | 87 |
Statin | 73 | 77 | 77 |
Glycoprotein IIb/IIIa inhibitor | 90 | 94 | 90 |
Abciximab | 63 | 62 | 67 |
Eptifibatide | 26 | 30 | 26 |
Tirofiban | 7.2 | 6.1 | 5.2 |
Unknown | 2.9 | 2.4 | 2.0 |
Clopidogrel | 94 | 94 | 95 |
Ticlopidine | 1 | 1 | 2 |

Data are medians (interquartile range) or percentages.

Figure 2. Complement inhibition as measured by hemolytic assays. Dots are mean values, vertical lines are median and interquartile ranges, and plot ends are minimum and maximum values.

Figure 3. Cumulative frequency distribution of creatine kinase-MB AUC by treatment.
inflammatory cytokines, enhanced nitric oxide synthase activity, and apoptosis. Pexelizumab inhibits the complement system at C5, preserving proximal C3a and C3b functions of bacterial opsonization and preventing terminal complement generation. Complement inhibition has reduced infarct size in various animal models, and, in a small human study of C1 inhibition, infarct size was limited compared with historical controls. In the ischemia/reperfusion setting of cardiopulmonary bypass surgery, pexelizumab appears to reduce cardiac enzyme release and possibly mortality (S. Sherman, MD, unpublished data, 2002).

C5 complement inhibition prevents apoptosis in animals, and significant apoptosis occurs during the first 2 weeks after MI in humans. C5a and C5b-9 also may affect remodeling by enhancing matrix-degrading enzymes. Inhibition of inducible nitric oxide synthase, especially in patients with large infarctions and cardiogenic shock, also is a promising target for improving outcomes. The effect on mortality in the days and weeks after MI suggests a reduction of delayed myocardial damage by an antiinflammatory effect and improved healing and remodeling through effects on mechanisms of cell death.

CARDINAL was designed as separate studies of fibrinolysis and primary PCI, anticipating possible differences in treatment effect, but the substantially reduced mortality with primary angioplasty but not with fibrinolysis was unexpected. The process and pattern of reperfusion differ with these strategies. Fibrinolytic-generated reperfusion tends to be gradual and often intermittent. With primary PCI, patency is abruptly—often more effectively—reestablished, as shown by the greater proportion of COMMA patients with complete early ST-segment resolution. However, primary PCI also is associated with distal embolization, particularly with stenting, which can cause endothelial dysfunction and microvascular inflammation. In COMMA, most patients had received both stents and glycoprotein IIb/IIIa inhibitors. That treatment effects may differ by reperfusion strategy is supported by the finding that abciximab, an agent with pleiotropic effects beyond platelet inhibition, reduces mortality in primary PCI but not in combination with fibrinolysis.

As in any phase II program, our trial was not powered to detect modest differences in clinical end points, including mortality. The large effect seen may represent an overestimate of a true treatment effect, although the benefit appeared early, persisted over time, and was accompanied by a trend in the bolus-only group. Infarct size measurement with CK-MB AUC in patients treated with reperfusion therapy may be imprecise, especially among patients with missing samples or high values at 72 hours.

In the COMMA trial, a significant reduction in mortality was observed, although the number of deaths was small and mortality was a secondary end point. For the first time, an adjunctive therapy to protect the myocardium during reperfusion has resulted in reduced mortality. These results suggest the need for additional investigation of pexelizumab as an adjunctive treatment for acute ST-segment-elevation MI, particularly in the setting of mechanical reperfusion.

Appendix

COMMA Steering Committee

TABLE 4. Follow-Up Data

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=242)</th>
<th>Bolus (n=247)</th>
<th>Bolus + Infusion (n=262)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical outcomes, 30 d</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reinfarction</td>
<td>0.8</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td>4.1</td>
<td>2.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5.8</td>
<td>3.2</td>
<td>5.3</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsustained</td>
<td>17.4</td>
<td>17.4</td>
<td>19.8</td>
</tr>
<tr>
<td>Sustained</td>
<td>1.2</td>
<td>2.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>2.5</td>
<td>2.8</td>
<td>2.7</td>
</tr>
<tr>
<td>Bradycardia (symptomatic)</td>
<td>3.3</td>
<td>4.9</td>
<td>5.3</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.8</td>
<td>0.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Intervventional procedures, 90 d</td>
<td>(n=271)</td>
<td>(n=262)</td>
<td>(n=282)</td>
</tr>
<tr>
<td>Repeat angiography</td>
<td>16.2</td>
<td>16.4</td>
<td>14.5</td>
</tr>
<tr>
<td>Repeat percutaneous procedure</td>
<td>9.6</td>
<td>10.7</td>
<td>12.1</td>
</tr>
<tr>
<td>Bypass surgery</td>
<td>7.0</td>
<td>5.3</td>
<td>6.4</td>
</tr>
<tr>
<td>ST-segment resolution (&gt;70%), 24 h</td>
<td>(n=229)</td>
<td>(n=240)</td>
<td>(n=250)</td>
</tr>
<tr>
<td>QRS score, day 6 or at discharge</td>
<td>(n=213)</td>
<td>5.91 (0.28)</td>
<td>5.96 (0.26)</td>
</tr>
<tr>
<td></td>
<td>(n=212)</td>
<td>6.22 (0.25)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=230)</td>
<td>6.22 (0.25)</td>
<td></td>
</tr>
</tbody>
</table>

Data are percentages or means (SE).

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Investigators
Numbers of patients enrolled are shown in parentheses.
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References

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