Pexelizumab for Acute ST-Elevation Myocardial Infarction in Patients Undergoing Primary Percutaneous Coronary Intervention

A Randomized Controlled Trial

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Context Reperfusion with percutaneous transluminal coronary intervention (PCI) is effective at improving outcomes in patients with acute ST-elevation myocardial infarction (STEMI). However, in patients without prompt reestablishment of brisk coronary flow and tissue perfusion, mortality remains high, providing an opportunity for novel treatments, including anti-inflammatory agents.

Objective To evaluate the effectiveness of pexelizumab, a humanized monoclonal antibody that binds the C5 component of complement, as an adjunct to PCI in improving 30-day mortality from STEMI.

Design, Setting, and Patients This trial was a prospective, multicenter, double-blind, placebo-controlled, phase 3 study of the intravenous administration of pexelizumab in conjunction with primary PCI in STEMI with prespecified high-risk electrocardiographic findings. The trial was intended to enroll 8500 patients, but in conjunction with the US Food and Drug Administration enrollment was modified to 5745 patients presenting from 296 hospitals in 17 countries from July 13, 2004, to May 11, 2006.

Interventions Two thousand eight hundred eighty-five patients were randomly assigned to receive placebo and 2860 to receive pexelizumab given as a 2-mg/kg intravenous bolus prior to PCI followed by 0.05-mg/kg per hour infusion over the subsequent 24 hours. Patients were randomized within 6 hours of symptom onset.

Main Outcome Measures The primary end point was all-cause mortality through day 30. Secondary end points were death through day 90 and the composite of death, cardiogenic shock, or congestive heart failure through days 30 and 90.

Results No difference in mortality through day 30 was observed between the pexelizumab and placebo treatment groups, with 116 patients (4.06%) and 113 patients (3.92%) who died in the respective groups (hazard ratio [HR], 1.04; 95% confidence interval [CI], 0.80-1.35; log-rank $P=.78$). The composite end points of death, shock, or heart failure were also similar with 257 patients (8.99%) receiving pexelizumab and 265 patients (9.19%) receiving placebo at 30 days (HR, 0.98; 95% CI, 0.83-1.16; $P=.81$) and 293 patients (10.24%) receiving pexelizumab and 293 patients (10.16%) receiving placebo at 90 days (HR, 1.01; 95% CI, 0.86-1.19; $P=.91$).

Conclusion In this large clinical trial of patients treated with primary PCI for STEMI, mortality was low and unaffected by administration of pexelizumab.

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ACUTE ST-ELEVATION MYOCARDIAL infarction (STEMI) constitutes a major public health problem, not only in western countries but increasingly in developing countries.[1] In the United States, there are estimated to be more than half a million STEMI events annually and these have provided strong impetus for efforts to improve both the process whereby care is delivered and the treatment elements administered.[2] Although reperfusion with primary percutaneous transluminal coronary intervention (PCI) is highly effective, especially if delivered promptly in an expert facility, it is now appreciated that not all PCIs adequately restore myocardial or tissue perfusion.[3] Reperfusion achieved through primary PCI and coronary stenting may be associated with distal coronary embolization, endothelial dysfunction, and impaired ventricular function.[4] A concomitant inflammatory reaction, participating in the accompanying reperfusion injury may mediate apoptosis in the peri-infarction area and unfavorable left ventricular remodeling.[5] Poor tissue perfusion and the intensity of the inflammatory response are related to subsequent mortality.[4,6]

Complement is known to be both activated and a potential mediator of these processes, and activation of the terminal components of the complement cascade leads to cleavage of the C5 component: this in turn results in formation of both C5a, a potent anaphylatoxin and proinflammatory substance, and C5b-9 or the membrane attack complex (MAC), which causes vesiculation of platelets and endothelial cells, formation of prothrombotic microparticles, and activation of leukocytes and endothelial cells. Hence, inhibition of C5 constitutes an attractive therapeutic target.[7]

For editorial comment see p 91.

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Pexelizumab, a humanized monoclonal antibody that binds to the C5 component of complement is known to inhibit apoptosis and leukocyte infiltration resulting in reduced infarct size in experimental model.[7,8] Although a phase 2 clinical study of 960 STEMI patients undergoing primary PCI did not achieve a reduction in MI size, the strategy of a pexelizumab bolus plus a 24-hour infusion favorably affected the incidence of mortality and cardiogenic shock.[9]

Given the desirability of treating the inflammatory components of STEMI along with the excellent safety and tolerability profile of pexelizumab given to populations who had experienced both prior MI and had undergone coronary artery bypass surgery, we undertook the current phase 3 investigation of adjunctive treatment with pexelizumab in STEMI patients undergoing primary PCI.[9,10]

METHODS

Patients

Between July 13, 2004, and May 11, 2006, we randomized 5745 patients from 17 countries and 296 sites in the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX AMI) trial. Eligibility for enrollment required patients to be at least 18 years of age and to present within 6 hours of symptoms that were deemed ischemic and that had persisted for at least 20 minutes. Patients were expected to undergo primary PCI and were required to have high-risk electrocardiographic characteristics: these included at least 2-mm ST elevation in 2 anterior lateral leads or at least 2-mm ST elevation in 2 inferior leads coupled with ST depression in 2 contiguous anterior leads for a total of 8 mm or more or a new left-bundle branch block with at least 1-mm concordant ST elevation.

Patients were excluded if they had isolated inferior MI, were pregnant or breastfeeding, had known or suspected complement deficiency or active serious infection, or had other serious medical conditions likely to alter their recovery. Prior fibrinolytic therapy for treatment of the qualifying event was also a basis for exclusion. No upper age limit was set. The institutional review board of each participating hospital approved the protocol, and patients were required to provide written informed consent.

Randomization

All randomization of patients and drug supply were managed by an interactive-voice-response system. A dynamic allocation algorithm using the Schouten method[11] was used through the voice-response system to randomly assign patients to receive either placebo or pexelizumab in a 1:1 ratio. Patients were stratified by location of MI (high-risk inferior or other MI location) and by site.

Interventions

Patients were to receive an intravenous bolus of 2 mg/kg of pexelizumab or matching placebo given in double-blinded fashion prior to PCI over 10 minutes followed by 0.05-mg/kg per hour infusion of pexelizumab or placebo as a continuous intravenous drip of 20 mL/h over the subsequent 24 hours. The pexelizumab dose chosen was previously used in the Complement Inhibition in Myocardial Infarction Treated With Angioplasty (COMMA) study and is known to produce near complete inhibition for 24 hours of complement activity by hemolytic assay.[9] Study medicine bolus was to be given before balloon inflation and/or stent placement. Concomitant medications and subsequent cardiac procedures were left to the discretion of the attending physician, but strong encouragement was provided to comply with the acute STEMI treatment guidelines established by the American College of Cardiology/American Heart Association/the European Society of Cardiology.[2,12]

Study Objectives

Our primary objective was to determine whether pexelizumab reduced all-cause mortality through day 30. Secondary objectives included evaluation of pexelizumab's effect on death as well as the composite incidence of death, cardiogenic shock, or congestive heart failure (CHF) through days 30 and 90. Tertiary objectives included stroke and recurrent MI at day 90; sepsis through hospital discharge or day 14, whichever occurred earlier; shock at day 30; and 90-day composites of cardiogenic shock or congestive heart failure, death or cardiogenic shock, and death or CHF.

Congestive heart failure and cardiogenic shock were centrally adjudicated by a clinical events committee blinded to treatment assignment.[13] Congestive heart failure included new or worsening CHF occurring during the index hospitalization or rehospitalization for CHF. New CHF during the index hospitalization was required to begin or persist more than 24 hours after randomization. Worsening CHF had to occur or persist for more than 24 hours after randomization. Congestive heart failure was defined on the basis of the physician's decision to treat CHF with an intravenous diuretic, inotropic agent, or vasodilator and at least 1 of the following: presence of pulmonary edema or pulmonary vascular congestion on chest radiograph believed to be of cardiac cause; rales reaching greater than a third up the lung fields believed to be due to CHF; pulmonary capillary wedge pressure or left ventricular end-diastolic pressure greater than 18 mm Hg; or dyspnea, with documented P_{O_2} less than 80 mm Hg on room air or oxygen saturation less than 90% on room air, without significant lung disease. Rehospitalization for CHF to an acute care facility primarily for the treatment of CHF had to include intravenous treatment of CHF with a diuretic, inotropic agent, or vasodilator.

Cardiogenic shock was defined as hypotension of less than 90 mm Hg systolic blood pressure lasting for at least 1 hour, not responsive to fluid resuscitation and/or heart rate correction, believed to be secondary to cardiac dysfunction, and associated with at least 1 of the following signs of

hypoperfusion: cool, clammy skin, oliguria, altered sensorium, cardiac index less than or equal to 2.2 L/min per meter squared.

Occurrence of other tertiary end points (eg, recurrent MI, bleeding, stroke, sepsis) were ascertained by site investigators. Recurrent MI within 24 hours of randomization was defined as reelevation of creatine kinase MB by 33% or more from the preceding value or 100% from the preceding nadir (which was ≥2 or ≤2 times the upper limit of normal, respectively) and reached a level of at least 3 times normal and accompanying ischemic symptoms. Recurrent MI after 24 hours from randomization was defined as new pathologic Q waves, reelevation of creatine kinase MB to at least 3 times (24 hours to discharge), or at least 2 times the upper limit of normal (after hospital discharge), and accompanying ischemic symptoms. Bleeding was classified according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria as mild, moderate, or severe.[14] Stroke was defined as a focal neurologic deficit with residual symptoms lasting more than 24 hours after onset. Adverse events were regularly monitored during hospitalization using a clinical-events check list and serious adverse-event log at discharge or day 14, whichever was earlier.

A subset of 229 APEX patients (2:1 pexelizumab to placebo) was sampled for pharmacodynamic assessment of complement suppression (hemolytic activity) at baseline and at 24 hours according to methods previously described.[9]

Power and Sample Size Considerations

We originally intended to enroll 8500 patients in APEX-AMI and follow up with them for a minimum of 90 days in order to achieve an 80% power on the originally planned primary end point of all-cause 90-day mortality.[14] This sample size assumed a placebo mortality of 6.5% and a treatment effect of 24% relative reduction by pexelizumab with an anticipated total number of deaths of 487. The protocol allowed for sample-size adjustment in consultation with the executive steering committee based on blinded event rates.

After approximately 26% of the total events had been accumulated, derived from a total of 3091 patients, a composite 90-day mortality of 4.1% was noted, which was substantially lower than that anticipated. It was then estimated that approximately 11 000 patients would be required as well as an additional 2 years of enrollment to achieve the original objective. Additionally, a contemporary systematic review of 4 placebo-controlled trials of pexelizumab in patients undergoing either acute MI or coronary bypass graft surgery revealed a 30% relative risk reduction ($P=.02$) in mortality at 30 days.[15] Subsequently preliminary results for the Pexelizumab for Reduction in Infarction and Mortality in Coronary Artery Bypass Graft surgery 2 (PRIMO CABG) trial were added to this overview resulting in a revised overall 24% relative risk reduction ($P=.009$) estimate for pexelizumab in 30-day mortality.[16] In conjunction with the sponsors and in consultation with the US Food and Drug Administration, an agreed upon revised study plan was formulated to continue the APEX-AMI trial until at least half of the anticipated number of events was accumulated. At that point, if the observed reduction in 30-day mortality was indeed 24% (ie, was consistent with the results of the systematic overview), the trial would produce a significant treatment difference ($P<.05$) with 52% power.[17]

Hence the primary efficacy analysis in APEX was based on all-cause 30-day mortality in all randomized patients and the intention-to-treat principle. For the primary efficacy analysis, patients were observed through 30 days and contacted primarily at both 30 and 90 days. Survival status data was 99.8% complete (only 2 patients were lost-to-follow up at 30 days) and subsequently 15 patients were lost to follow up at 90 days. The statistical assessment of treatment differences in mortality was performed using 2-sided testing based on the log-rank statistic and a significance level of $\alpha = .05$. Cumulative event rates were calculated according to the Kaplan-Meier method. Event (or censoring) times for all patients were measured from the time of randomization (time 0). Treatment differences were descriptively summarized as hazard ratios with associated confidence intervals derived from the Cox proportional hazards model. For selected secondary outcomes for which timing of the events was not available, risk reductions and 95% confidence intervals (CIs) were based on Mantel-Haenszel statistics, and the associated *P* values were based on Fisher exact test analysis summarized by hazard ratios (HRs) and 95% CIs was prespecified for subgroups defined by geographic regions (North America, Australia and New Zealand, and Western and Eastern Europe), sex, age, baseline Killip class, heart rate, systolic blood pressure, MI location, diabetes, baseline serum enzymes or markers, and history of prior MI.

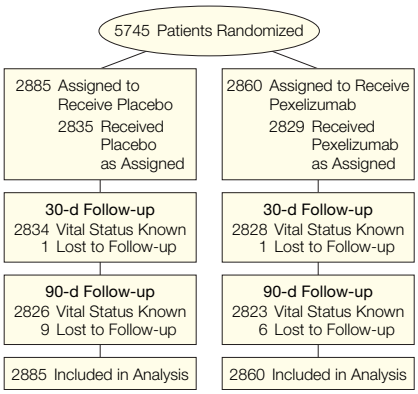
The defined blinded database that was housed in the Biometric Division of Procter & Gamble was unblinded on June 27, 2006, and shared simultaneously with the academic research organization (Virtual Coordinating Center for Global Collaborative Cardiovascular Research [VIGOUR] and the Duke Clinical Research Institute) for confirmation of the final results, which was undertaken October 29, 2006. The APEX academic leadership had full access and primary responsibility for presentation and publication of the data.

The study had an independent data and safety monitoring board responsible for evaluating the safety and efficacy aspects of the trial on an ongoing basis. Only 1 interim analysis was performed by the data and safety monitoring board after 25% of the events had occurred. The design for interim analysis included the use of asymmetric moni-

toring boundaries for which the upper boundary for efficacy was an O'Brien-Fleming boundary generated using the Lan-DeMets α-spending function whereas the lower boundary was based on a linear α-spending function.[18,19]

An executive and steering committee as well as the data safety and monitoring board and clinical events committee oversaw all aspects of APEX-AMI. The independent data and safety monitoring board evaluated the safety and efficacy aspects of the trial on an ongoing basis. The independent clinical events committee adjudicated all suspected CHF and shock events using specific end point criteria previously described. SAS version 8.2 software (SAS Institute Inc, Cary, NC) was used to conduct all the statistical analyses.

Figure 1. Patient Flow Diagram



RESULTS

A flowchart of patient disposition is illustrated in FIGURE 1. Adherence to the protocol was excellent, and only 81 patients did not receive study drug and only 380 did not undergo primary PCI.

In TABLE 1, the baseline characteristics of the study population are shown. In general, placebo and pexelizumab groups were well matched and represent the usual characteristics of a STEMI population. There were slightly more women in the group assigned to pexelizumab. By design, because inferior MIs were required to be at high risk based on their admission electrocardiogram results, 41% of the population were so characterized. Approximately 30% of patients were randomized within the United States and the remainder in Europe, Australia, New Zealand, and Canada.

In TABLE 2, details regarding the timeliness of reperfusion with PCI and procedural outcomes are outlined. Patients received treatment in a reasonably timely fashion with median first door to balloon times of 1.6 hours (interquartile range, 1.08-2.22 hours); for the 36% of patients transferred to a PCI from another facility, this time was 2.2 hours, and for those directly admitted to a PCI hospital, it was 1.3 hours. These times were well balanced between treatment groups. There was also a short interval, ie, 15 minutes between study bolus and PCI, and a high degree of procedural success as reflected by Thrombolysis in MI (TIMI) 3 flow (87%). Intracoronary stent usage (89%) was frequent and evenly balanced both for bare-metal and drug-eluting types.

In TABLE 3, concomitant medications used are depicted according to in hospital and those prescribed at discharge. This confirms excellent adherence to evidence-based therapies known to enhance outcome following STEMI. In particular, there was high use of thienopyridine platelet inhibitors and more than two thirds of patients received glycoprotein IIb/IIIa inhibitors in conjunction with PCI.

In FIGURE 2 and TABLE 4, the primary result (ie, 30-day mortality) is shown. There was no difference be-

Table 1. Baseline Characteristics According to Randomized Study Assignment*

Parameter	Placebo (n = 2885)	Pexelizumab (n = 2860)
Age, y		
Median (IQR)	61 (52-71)	61 (51-71)
≥75, %	479 (16.6)	498 (17.4)
Women, No. (%)	634 (22.0)	691 (24.2)
Weight, median (IQR), kg	80 (70-91)	80 (70-91)
Heart rate, median (IQR), beats/min	75 (64-86)	75 (65-86)
Systolic blood pressure, median (IQR), mm Hg:	133 (117-150)	133 (117-150)
Killip class, No. (%)†		
I	2580 (89.6)	2548 (89.2)
II	236 (8.2)	253 (8.9)
III	33 (1.2)	31 (1.1)
IV	32 (1.1)	26 (0.9)
Infarct location, No. (%)		
Inferior	1180 (40.9)	1167 (40.8)
Clinical history, No. (%)		
Prior MI	354 (12.3)	340 (11.9)
Prior CHF	103 (3.6)	105 (3.7)
Prior stroke	99 (3.3)	117 (4.1)
Prior CABG	68 (2.4)	60 (2.1)
Prior PCI	284 (9.9)	278 (9.7)
History of diabetes	467 (16.2)	446 (15.6)
Current smoker‡	1252 (43.6)	1226 (42.9)
Creatinine clearance, median (IQR), mL/min	82.7 (63.7-107.8)	83.0 (64.1-105.8)
Geographic region, No. (%)		
North America	1043 (36.2)	1043 (36.5)
Western Europe	888 (30.8)	876 (30.6)
Eastern Europe	667 (23.1)	670 (23.4)
Australia or New Zealand	287 (9.9)	271 (9.5)

Abbreviations: CABG, coronary artery bypass graft surgery; CHF, congestive heart failure; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention.
*Percentages may not sum to 100 due to rounding.
†Data unavailable for 6 patients: 4 in the placebo group and 2 in the pexelizumab group.
‡Data unavailable for 15 patients: 10 in the placebo group and 5 in the pexelizumab group.

tween placebo and pexelizumab treated patients, ie, each experiencing a low mortality of 3.92% and 4.06%, respectively (HR, 1.04; 95% CI, 0.80-1.35; log-rank $P=.78$). In Figure 2 and Table 4, the 30-day composite end point of death, cardiogenic shock, or heart failure is shown and was also similar between treatment groups (9.19% for placebo and 8.99% for pexelizumab (HR, 0.98; 95% CI, 0.83-1.16; log-rank $P=.81$) . At 90 days (FIGURE 3) mortality remained low and similar in both treatment groups, ie, 4.51% and 4.93% for placebo and pexelizumab, respectively. The composite end point of death, shock, or heart failure (Figure 3) was also similar at day 90, 10.16% and 10.24% for placebo and pexelizumab (HR, 1.01; 95% CI, 0.86-1.19; log-rank $P=.91$).

Subgroup analyses showed no significant heterogeneity of treatment effect according to, age, sex, baseline Killip class, systolic blood pressure, diabetes, baseline enzymes or markers, and history of prior MI. Because MI location was a variable used for stratification, we observed a 30-day mortality for inferior MI of 2.5% for placebo and 3.0% for pexelizumab (HR, 1.18; 95% CI, 0.7-1.9; log rank $P=.50$) and for other MI, this was 4.9% for placebo and 4.8% for pexelizumab (HR, 0.92; 95% CI, 0.7-1.13; log rank $P=.92$).

In Table 4, other relevant clinical outcomes are shown as predetermined by protocol. The incidence of heart failure and shock was equally balanced and low as was the incidence of recurrent MI and stroke. Although infrequent, renal failure was balanced between treatment groups. In spite of the theoretical possibility of more infection with a complement inhibitor,

Table 2. Timeliness and Procedural Details According to Randomized Study Assignment

	Placebo (n = 2885)	Pexelizumab (n = 2860)
Symptom onset to enrollment, median (IQR), h	2.75 (2.0-3.95)	2.78 (2.0-3.97)
Symptom onset to PCI, median (IQR), h	3.33 (2.52-4.57)	3.35 (2.50-4.50)
Door to PCI, median (IQR), h	1.62 (1.08-2.22)	1.58 (1.12-2.23)
Study drug to PCI, median (IQR), h	0.23 (0.12-0.42)	0.25 (0.12-0.42)
Study drug infusion, mean (SD), h	23.67 (2.85)	23.6 (3.15)
Procedural outcomes, No. (%)		
TIMI-3 flow	2482 (86.03)	2491 (87.10)
TIMI-2 flow	198 (6.86)	167 (5.84)
Stent usage, No. (%)	2561 (88.77)	2563 (89.62)
Drug-eluting	1065 (36.92)	1079 (37.73)
Bare metal	1460 (50.61)	1443 (50.45)
Drug-eluting and bare metal	36 (1.25)	41 (1.43)

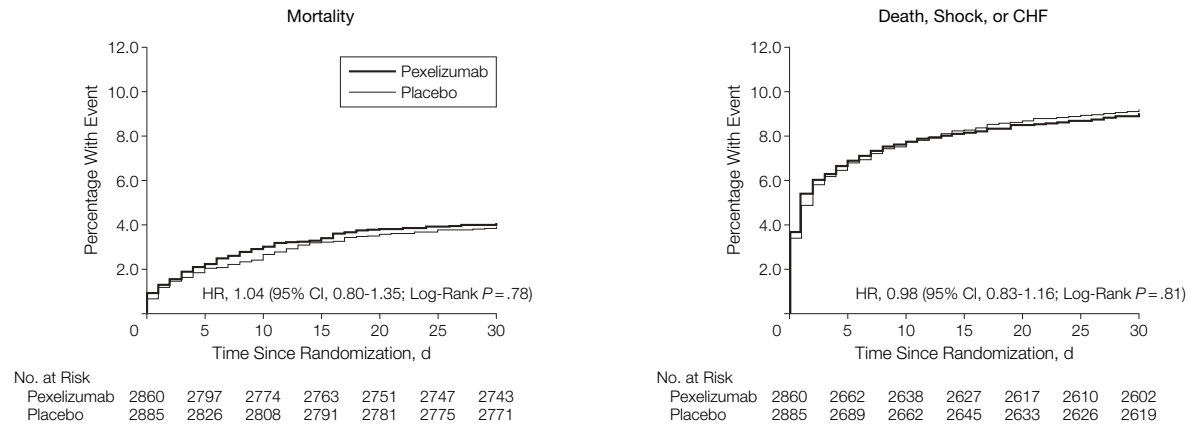
Abbreviations: IQR, interquartile range; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

Table 3. Concomitant Treatments According to Randomized Study Assignment and Time During Care

	No. (%)			
	Placebo (n = 2885)		Pexelizumab (n = 2860)	
	In Hospital	Discharge	In Hospital	Discharge
Aspirin	2802 (97.1)	2733 (94.7)	2771 (96.9)	2689 (94.0)
Thienopyridine agents	2673 (92.7)	2520 (87.3)	2648 (92.6)	2508 (87.7)
Statin	2626 (91.0)	2629 (91.1)	2602 (91.0)	2606 (91.1)
β-Blocker	2442 (84.6)	2527 (87.6)	2426 (84.8)	2507 (87.7)
ACE inhibitor	2290 (79.4)	2217 (76.8)	2268 (79.3)	2210 (77.3)
Glycoprotein IIb/IIIa inhibitors	1994 (69.1)	NA	1994 (69.7)	NA

Abbreviations: ACE angiotensin-converting enzyme; NA, not available.

Figure 2. Thirty-Day Mortality and Death, Shock, or Congestive Heart Failure



CHF indicates congestive heart failure; CI, confidence interval; and HR, hazard ratio.

we observed that sepsis, while uncommon in both groups, tended to be less common in patients treated with pexelizumab than with placebo (0.56% vs 0.90%; $P=.13$).

Overall, there were no safety concerns identified with pexelizumab. Major and minor bleeding was infrequent and similar between the 2 groups as were the numbers of serious adverse events reported in the 2 treatment groups.

To evaluate the biological activity of pexelizumab, pharmacodynamic analyses from a subgroup of 229 APEX patients (2:1 pexelizumab to placebo) were performed and confirmed that 90% of pexelizumab-treated patients achieved more that 70% complete inhibition of hemolytic activity at baseline and at 24 hours, similar to prior data from the COMMA study.[9]

Table 4. Clinical Outcomes According to Randomized Study Assignment

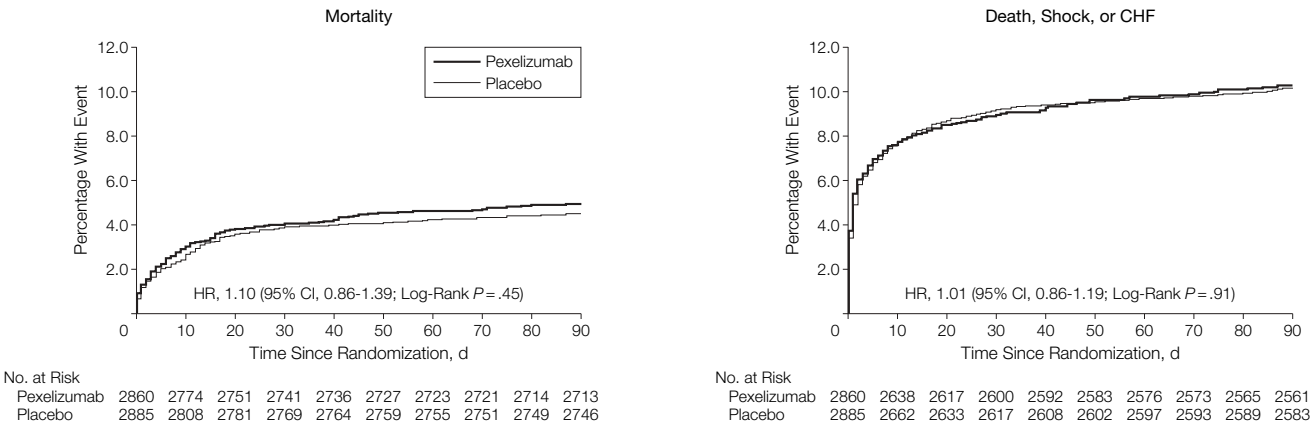
	No. (%)			
	Placebo (n = 2885)	Pexelizumab (n = 2860)	HR (95% CI)	*P* Value*
Death				
30 days	113 (3.92)	116 (4.06)	1.04 (0.80-1.35)	.78
90 days	130 (4.51)	141 (4.93)	1.10 (0.86-1.39)	.45
Death, shock, or CHF				
30 days	265 (9.19)	257 (8.99)	0.98 (0.83-1.16)	.81
90 days	293 (10.16)	293 (10.24)	1.01 (0.86-1.19)	.91
CHF				
30 days	116 (4.02)	114 (3.99)	0.99 (0.77-1.29)	.96
90 days	139 (4.82)	136 (4.76)	0.99 (0.78-1.25)	.92
Cardiogenic shock				
30 days	98 (3.40)	95 (3.32)	0.98 (0.74-1.30)	.88
90 days	100 (3.47)	96 (3.36)	0.97 (0.73-1.28)	.82
Recurrent MI 90 days	69 (2.39)	87 (3.04)	1.28 (0.93-1.75)	.13
Stroke 90 days	34 (1.18)	39 (1.36)	1.10 (0.86-1.39)	.53
Sepsis 14 days	26 (0.90)	16 (0.56)	0.62 (0.33-1.16)	.13
			RR (95% CI)	
Serious infection 14 days	73 (2.53)	65 (2.27)	0.90 (0.65-1.25)	.55
Bleeding 14 days				
Moderate	134 (4.64)	120 (4.20)	0.90 (0.71-1.15)	.44
Severe	19 (0.66)	19 (0.66)	1.01 (0.54-1.90)	>.99
Renal failure 14 days	55 (1.91)	44 (1.54)	0.81 (0.54-1.20)	.31

Abbreviations: CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; RR, relative risk.
*HRs (95% CIs) are based on the Cox proportional hazards model and the associated *P* values are based on log-rank statistic. RRs (95% CIs) are based on Mantel-Haenszel statistic and the associated *P* values are based on the Fisher exact test.

COMMENT

These data, acquired from the largest clinical trial of PCI-treated STEMI patients to date, show that pexelizumab does not affect the mortality or morbidity of a population presenting within 6 hours of symptom onset. Moreover we demonstrate that despite targeting a cohort for higher risk based on admission electrocardiographic findings and without conventional exclusion criteria, such as prior stroke, renal failure, increased bleeding risk, or shock on admission, the morbidity and mortality experienced in both treated and placebo groups was remarkably low. These excellent clinical outcomes from a large international study in which 36% of patients were transferred from a non-PCI to a PCI hospital and in whom overall first-door to PCI time was approximately 1.6 hours likely reflect the composite benefit derived from a coherent investigative team of physicians, nurses, and paramedics collaborating to deliver prompt and high-quality coronary intervention to their patients. In addition, the high degree to which evidence-based, guideline-recom-

Figure 3. Ninety-Day Death and Death, Shock, or Congestive Heart Failure



CHF indicates congestive heart failure; CI, confidence interval; and HR, hazard ratio.

mended concomitant medications were used, both during and after hospitalization, likely contributed to the low event rates.

Inflammation is important not only in the pathogenesis of atherosclerosis and plaque rupture leading to acute MI but also in the subsequent microcirculatory dysfunction and recovery following ischemia and reperfusion.[7] The complement system plays an important role in the inflammatory response, and its activity increases in infarcted tissue in the 24 to 48 hours after MI.[6] Ischemia and reperfusion experimental models show that inhibiting complement component C5 results in reduced infarct size and less apoptosis.[7]

Pexelizumab has been shown to reduce the amount of myocardial damage in the setting of coronary bypass graft surgery in 1 large trial (PRIMO 1) without a significant effect in a second large trial (PRIMO 2) but with a tendency for lower mortality in both.[10,16] In a phase 2 trial of acute MI treated with primary angioplasty, pexelizumab resulted in a statistically significant reduction in mortality but no reduction in infarct size assessed by creatine kinase MB.[9]

What might account for the failure to demonstrate a treatment effect of pexelizumab given the promising prior experimental work, phase 2 data in STEMI patients treated with PCI, and the systematic overview indicative of a mortality benefit in both STEMI and patients undergoing coronary artery bypass? The low morbidity and mortality of the APEX placebo patients were not foreseen. Mortality was substantially lower than in previous international trials focused on high-risk STEMI patients, including the COMMA trial conducted 4 years earlier. Moreover we specifically sought higher risk characteristics in APEX with the aim of achieving a 6.5% placebo mortality at 90 days. Hence, our ability to show a treatment effect was attenuated. Given the 95% CI includes the possibility of a 20% relative risk reduction with pexelizumab, it is possible that a treatment benefit was missed. In view of the overall result, however, it seems unlikely that continuing to enroll to achieve the projected 487 deaths, approximately 11 000 patients according to our original design, would have led to a different conclusion.

The trend toward less sepsis in pexelizumab-treated patients is also consistent with prior clinical studies and suggests that a biologic effect of study drug, thought to be mediated by enhanced clearance of opsonized bacteria, was operative.[10] The prior overview of trials of pexelizumab that showed a 30% risk reduction in 30-day mortality made the assumption that pexelizumab had similar effects in acute MI and in coronary artery bypass graft surgery (comprising the majority of the sample), which may not be the case.[15] When the preliminary results from PRIMO CABG 2 are added to this overview, a 24% reduction ($P = .009$) in 30-day mortality was evident. Finally it is possible that the positive phase 2 COMMA data represent the play of chance and provided too optimistic a projection of the treatment effect.[9]

Two prior phase 2 clinical studies have explored the anti-inflammatory hypothesis in STEMI by inhibiting white blood cell adhesion. The Limitation of MI following thrombolysis in AMI (LIMIT) trial evaluated 2 doses of therapy with a monoclonal antibody to the CD 18 subunit of β_2 integrin adhesion receptors.[20] Despite the anticipated induction of peripheral leucocytosis, no effect was observed on the primary end point of infarct size contrary to earlier experimental findings. In the Hu23F2G Anti-adhesion to limit cytotoxic injury following AMI (HALT-MI) study, 2 doses of a humanized antibody directed against all isoforms of the CD 11/CD 18 integrin receptor were evaluated in STEMI patients reperfused with primary PCI within 6 hours of symptom onset. Once again no effect on infarct size or clinical event was found.[21] In aggregate, these trials challenge the hypothesis that interfering with the inflammatory response will reduce infarct size and improve outcome in acute MI.

It remains unclear whether other myocardial protection strategies including anti-inflammatory, antiapoptotic, or metabolic manipulation might be successful. Whereas a proinflammatory state relates to worse outcomes, and we have previously shown that it can be modified by pexelizumab, the extent to which inflammation is caused by vs contributes to myocardial damage is unknown.[6] Timing of administration of therapies and targeting high-risk patients most likely to benefit are likely important variables in the modulation of inflammation in the clinical setting.[22] The lack of benefit or pexelizumab in APEX underscores the challenge of translating promising experimental treatments for myocardial protection to the clinic. In part, this could relate to redundancy in the inflammatory processes accompanying human MI or a limited tissue penetration of treatments despite evidence of their effects in blood.

In this large clinical trial of STEMI patients treated with primary PCI and usage of evidence-based therapies, mortality was low and unaffected by administration of pexelizumab.

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—Clarence Day (1874-1935)