Inhibition of complement activation by pexelizumab reduces death in patients undergoing combined aortic valve replacement and coronary artery bypass surgery

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Objective: We sought to evaluate the effects of pexelizumab, a C5 complement inhibitor, on death and myocardial infarction in patients undergoing combined aortic valve replacement and coronary artery bypass grafting surgery.

Methods: The Pexelizumab for Reduction in Myocardial Infarction and Mortality in Coronary Artery Bypass Graft surgery trial, a phase III prospective, randomized, double-blind, placebo-controlled study, enrolled 3099 patients at 205 centers. The primary end point was the composite of death, myocardial infarction, or both at postoperative day 30 in patients undergoing coronary artery bypass grafting without valve surgery. Postoperative myocardial infarction was defined as a creatine kinase MB fraction value of 100 ng/mL or greater, Q-wave myocardial infarction with a creatine kinase MB fraction value of 70 ng/mL or greater, or new Q-wave evidence of myocardial infarction by postoperative day 30. Because patients undergoing coronary artery bypass grafting with a valve procedure were not included in the primary population, separate analysis of death and myocardial infarction was conducted in 218 patients undergoing combined aortic valve replacement and coronary artery bypass grafting surgery.

Results: Of the 353 patients randomized to any valve procedure, 106 (61%) underwent combined aortic valve replacement and coronary artery bypass grafting in the pexelizumab treatment group compared with 112 (63%) patients in the placebo group. Coronary artery bypass grafting was performed with 1 or more internal thoracic artery grafts in 139 (64%) patients and with 1 or more saphenous vein grafts in 179 (82%) patients. There were 4 (3.8%) deaths in the pexelizumab group versus 11 (9.9%) in the placebo group by postoperative day 30 and 6 (5.7%) deaths in the active group versus 16 (14.4%) in the placebo group by postoperative day 180 ($P = .107$ and $P = .043$, respectively, Fisher exact test). The incidence of myocardial infarction 30 days after surgical intervention was identical in the 2 groups, but the study was not designed to detect differences in this cohort of patients.

Conclusions: Inhibition of complement activation by pexelizumab resulted in a decreased mortality at 180 days among 218 patients who underwent combined aortic valve replacement and coronary artery bypass grafting surgery. Additional studies are warranted to confirm this decrease in mortality with pexelizumab in combined aortic valve replacement and coronary artery bypass grafting procedures.

Pexelizumab is a novel recombinant, single-chain, and humanized anti-C5 monoclonal antibody fragment recently shown to decrease myocardial infarction (MI) and mortality rates after coronary artery bypass grafting (CABG).¹ Experimental evidence suggests that inhibition of C5 conversion to C5a

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and C5b can decrease the inflammatory reaction related to cardiopulmonary bypass (CPB) and reperfusion of ischemic myocardium.^{2,3} Human studies have also shown a beneficial effect of C5 inhibition on inflammation markers, MI rate determined on the basis of creatine kinase MB fraction (CK-MB), and postoperative death in that setting.⁴

The Pexelizumab for Reduction in Infarction and Mortality in Coronary Artery Bypass Graft surgery (PRIMO-CABG) trial enrolled 3099 patients, of whom 218 underwent combined aortic valve replacement (AVR) and CABG⁵ between January 2002 and February 2003. Patients undergoing combined valve and coronary artery surgery represent a complex subgroup of patients at a much higher risk for morbidity and mortality after surgical intervention compared with patients undergoing isolated CABG. The present study analyzes results of a subgroup of patients of the PRIMO-CABG trial. Patients who underwent combined AVR and CABG and who were recruited in the PRIMO-CABG trial formed the present group of interest for the study.

Patients and Methods

Patient Population

The study population, design, and main findings of the PRIMO-CABG trial have already been published.⁵ In summary, the trial was conducted at 205 sites in North America and Western Europe. Eligible patients included those scheduled for CABG with or without concurrent valve surgery. The study included patients with one or more of the following baseline risk factors: urgent intervention, diabetes mellitus, female sex, prior CABG procedure, history of a neurologic event, history of congestive heart failure (New York Heart Association class III or IV), or history of 2 or more MIs (excluding patients who have had an MI within 48 hours of CABG) or an MI that occurred 48 hours or more but 4 or fewer weeks before CABG. Exclusion criteria included planned aortic dissection repair, required aortic root reconstruction, or both; required salvage intervention; current cardiogenic shock; acute left ventricular, septal, or acute papillary muscle rupture; uncontrolled diabetes; history of renal failure and a serum creatinine value of greater than 3.0 mg/dL; history of chronic hepatic failure, hepatic cirrhosis, or both; and a history of malignancy, known or suspected hereditary complement deficiency, and any active infection. The institutional review boards or equivalent approved the protocol at each site, and all patients provided written consent.

Study Protocol

Patients were randomized in a double-blind fashion to receive either intravenous pexelizumab (2.0 mg/kg bolus followed by 0.05 mg · kg⁻¹ · h⁻¹ infusion for 24 hours) or placebo (placebo bolus followed by 24-hour infusion). Stratification occurred within each site and was based on whether valve surgery was planned, the type of valve surgery performed (mitral or other valve), and whether primary or repeat CABG was scheduled. Pexelizumab or placebo bolus was administered as soon as possible after anesthesia induction but no later than 10 minutes before CPB. Patients were followed for in-hospital adverse events and clinical end points. In

Abbreviations and Acronyms

AVR	= aortic valve replacement
CABG	= coronary artery bypass grafting
CK-MB	= creatine kinase MB fraction
CPB	= cardiopulmonary bypass
MI	= myocardial infarction
POD	= postoperative day
PRIMO-CABG	= Pexelizumab for Reduction in Infarction and Mortality in Coronary Artery Bypass Graft surgery

addition, patients were seen 14, 30, and 90 days after CABG surgery for adverse events and clinical outcomes and were contacted by telephone at 6 months to determine survival status.

Study End Points

For the present study focusing on patients undergoing AVR and CABG, death, MI, and complications were analyzed 30 and 90 days after surgical intervention, and survival status was also studied at 180 days. Death was defined as all-cause mortality. MI included both Q-wave and non-Q-wave MIs. A clinical events committee consisting of 3 expert cardiologists blinded to patient treatment assignment adjudicated all MIs. Through postoperative day (POD) 4, the diagnosis of a Q-wave MI required a new Q-wave persisting through POD 30 or associated with a peak CK-MB value of 70 ng/mL or greater; non-Q-wave MI required a peak CK-MB value of 100 ng/mL or greater within 96 hours postoperatively and without a new Q-wave. CK-MB measurements were collected at 4, 8, 12, 16, 24, 72, and 96 hours postoperatively and analyzed at a central core laboratory. Troponin I measurements were collected immediately before surgical intervention and on days 1, 2, and 4 after surgical intervention. Electrocardiograms were recorded at patient enrollment, as well as 48 and 96 hours and 14, 30, 90, and 180 days postoperatively. All electrocardiograms for the primary end point and prespecified secondary analyses were read at a central core laboratory. The pharmacodynamic effect of pexelizumab (inhibition of serum complement activity) was determined by using a standard total serum complement assay, as previously described.⁶

Statistical Analyses

The present report focused solely on patients recruited in the trial who underwent combined AVR and CABG. Patients who underwent isolated CABG and those who underwent CABG with another valve procedure at surgical intervention were excluded. The Wilcoxon rank sum test was performed on continuous data, and the Fisher exact test was used in comparing incidence rates. Survival analysis included Kaplan-Meier curve estimation.

Results

Patient Characteristics and Operative Data

Of the 218 patients undergoing AVR and CABG, 106 were randomized to receive intravenous administration of pexelizumab during the first 24 hours after surgical intervention

TABLE 1. Patient characteristics

	Pexelizumab (n = 106)	Placebo (n = 112)	P value
Age (y)	73 ± 8	73 ± 9	.635
Female sex	39 (37%)	43 (38%)	.889
NYHA class III and IV	43 (41%)	53 (48%)	.341
Aortic valve insufficiency	8 (7.5%)	12 (10.7%)	.486
Reoperative CABG	15 (14%)	15 (13%)	1.000
Prior myocardial infarction	20 (18.9%)	27 (24.1%)	.411

NYHA, New York Heart Association; CABG, coronary artery bypass graft surgery.

TABLE 2. Operative data

	Pexelizumab (n = 106)	Placebo (n = 112)	P value
Crossclamp time (min)	106 ± 3	107 ± 3	.979
CPB time (min)	146 ± 5	147 ± 4	.870
ITA grafts	66 (62%)	73 (65%)	.675
SV grafts	92 (87%)	87 (78%)	.111
No. of coronary artery grafts per patient	2.4	2.2	.336

CPB, Cardiopulmonary bypass; ITA, internal thoracic artery; SV, saphenous vein.

TABLE 3. Adverse events and infection logs through 90 days

	Pexelizumab (n = 104)	Placebo (n = 110)	P value
Atrial fibrillation	28 (26.9%)	30 (27.3%)	1.000
Pleural effusion	26 (25%)	26 (23.6%)	.874
Acute renal failure	4 (3.8%)	4 (3.6%)	1.000
Cardiac tamponade	3 (2.9%)	2 (1.8%)	.676
Complete AV block	3 (2.9%)	1 (0.9%)	.358
Septicemia	2 (2%)	11 (10.2%)	.019
Endocarditis	0	1 (0.9%)	1.000
Pneumonia	4 (3.9%)	13 (11.9%)	.042
Sternal wound infection			
Superficial	2 (2%)	4 (3.7%)	.684
Deep	2 (2%)	1 (0.9%)	.61
Wound infection at the leg vein harvesting site	10 (9.8%)	5 (4.6%)	.18
Urinary tract infection	6 (5.9%)	17 (15.7%)	.001
Stroke	2 (1.9%)	9 (8.2%)	.06

AV, Atrial ventricular.

compared with 112 patients undergoing the same procedure who were allocated to the placebo group. Patients in both groups were mostly male and averaged 73 years old. Aortic stenosis was the main indication for AVR in the 2 groups of patients. Fourteen percent and 13% of the patients, respectively, underwent reoperative CABG (Table 1).

The average crossclamp and CPB times were similar in the 2 groups. The use of internal thoracic artery and saphenous vein grafts was also similar between the 2 groups (Table 2).

Adverse Events and Pharmacodynamics

The most common adverse events reported were atrial fibrillation and pleural effusion, with a similar incidence reported between groups (Table 3). Of interest, septicemia

and pneumonia were more frequent in the placebo group compared with in the pexelizumab group. Endocarditis and sternal wound infection rates were similar in the 2 groups. Stroke rates were not statistically different between the 2 groups. Pexelizumab bolus and 24-hour infusion resulted in an inhibition of total serum complement hemolytic activity, which recovered to baseline levels 72 hours after surgical intervention (Figure 1).

Clinical Outcomes

Four patients (4/106 [3.8%]) in the pexelizumab group and 11 (11/112 [9.9%]) in the placebo group died within the first 30 days after surgical intervention ($P = .107$), suggesting a 62%, albeit not statistically significant, reduction in death

Figure 1. Serum complement activity measure with a standard complement hemolysis assay. * $P < .01$ between the 2 groups at 4 and 24 hours, Wilcoxon rank sum test.

Figure 2. Actuarial survival.

with pexelizumab. In the pexelizumab group 22 (22/106 [21%]) patients and in the placebo group 23 (23/112 [21%]) patients met the previously defined criteria for postoperative MI within the first 30 days after surgical intervention ($P = 1.000$). Q-wave MI was documented in 7 (7/106 [6.6%]) and 3 (3/112 [2.7%]) patients, respectively ($P = .205$). Non-Q-wave MI was documented in 15 (15/106 [14.2%]) and 20 (20/112 [17.9%]) patients, respectively ($P = .64$). The composite of death, MI, or both occurred in 23 patients (23/106 [22%]) in the pexelizumab group and in 31 patients (31/111 [28%]) in the placebo group ($P = .44$).

At 90-day follow-up, 5 patients (5/106 [4.7%]) in the pexelizumab group and 15 patients (15/112 [13.5%]) in the control group had died ($P = .034$). Pexelizumab reduced the risk of death by 65%. At 180-day follow-up, mortality rates averaged 5.7% (6/106) and 14.4% (16/112), respectively ($P = .043$), a risk reduction of 60% among patients treated with pexelizumab (Figure 2).

The causes of death at 180-day follow-up among pexelizumab-treated patients were MI in 2 patients, renal failure in 1 patient, disseminated intravascular coagulation in 1 patient, multiorgan failure in 1 patient, and an unspecified cause in a last patient. Among the latter patients, one death from MI occurred at POD 31, and another occurred at POD 88 from renal failure. In the placebo group the causes of death at 180-day follow-up were cerebral complication (stroke and bleeding) in 3 patients, sepsis in 3 patients, respiratory failure in 2 patients, congestive heart failure in 2 patients, renal failure in 1 patient, cardiogenic shock in 1 patient, multiorgan failure in 1 patient, pulmonary artery trauma at surgical intervention in 1 patient, sudden cardiac death in 1 patient, and a noncardiac cause in a last patient. Among the latter patients, 1 patient died from cerebral complication at POD 32 after surgical intervention, 1 pa-

tient died from sepsis at POD 46, 1 patient died from renal failure at POD 71, 1 patient died from cardiac arrest at POD 83, and 1 patient died from a non-cardiac-related cause 158 days after surgical intervention.

Discussion

The present study showed that inhibition of complement activation by pexelizumab resulted in a decreased mortality at 90 and 180 days among patients who underwent combined AVR and CABG surgery. An important mechanism of cardiac injury during cardiac surgery is the excessive activation of the complement cascade related to ischemia and reperfusion, contact activation, and general systemic inflammation from CPB. Pexelizumab, a humanized anti-C5 complement antibody fragment, prevents cleavage of C5, thus mitigating the effects of the terminal complement components C5a and C5b-9 on vascular permeability, chemoattraction, and cellular activation, with subsequent cytokine release that might result in myocardial cell damage, systemic inflammation, and apoptosis.³

Fitch and colleagues⁴ first reported that sC5b-9, leukocyte activation through CD11b expression, myocardial injury determined on the basis of CK-MB measurements, and cognitive deficits determined with preoperative and postoperative tests were significantly reduced in patients who received pexelizumab. These authors have established that effective inhibition of human C5 has a profound anti-inflammatory effect on patients undergoing CABG with CPB.

In a phase II prospective, multicenter, randomized, placebo-controlled trial, Shernan and associates¹ suggested that MI and mortality could be decreased with pexelizumab in patients undergoing CABG. The PRIMO-CABG trial then enrolled 3099 patients: 2732 (88%) underwent isolated CABG, and 353 (11%) underwent combined valve surgery

plus CABG, including 218 (7%) undergoing AVR plus CABG. The primary end point of combined death or MI 30 days after surgical intervention was reduced by 18% in patients undergoing isolated CABG treated with pexelizumab. Pexelizumab was associated with a significant decrease in death or MI rate 180 days after surgical intervention. Although the study was not powered for detecting differences in mortality, death alone was not affected by pexelizumab in patients undergoing isolated CABG.

Compared with patients undergoing isolated CABG, our subgroup of patients undergoing AVR plus CABG was older, had a greater proportion of repeat CABG, and was less likely to have experienced a preoperative MI. Of interest, mortality at 90 and 180 days after surgical intervention was decreased in patients treated with pexelizumab in our substudy patients who underwent combined AVR and CABG.

Several studies have reported difficulties in obtaining optimal myocardial protection during AVR because of associated left ventricular hypertrophy.⁷ Shernan and associates¹ show that patients undergoing AVR plus CABG release more CK-MB after surgical intervention than patients undergoing isolated CABG (median CK-MB peak release of 50 ng/mL vs 30 ng/mL, respectively). The greater release of CK-MB after AVR explains the high rate of MI reported in these patients compared with that seen in patients undergoing isolated CABG. The high rate of MI in the 2 groups (45/218 [21%]), although mostly non-Q-wave, is related to the definition of postoperative MI based on the experience gained with the study of patients undergoing isolated CABG. Although Klatte and coworkers⁸ showed a relation between the release of CK-MB after isolated CABG and 6-month mortality in studying patients in the Guardian trial, whether this link is applicable to patients undergoing AVR remains to be proved.

The important limitation of the present study remains related to the subanalysis of the main trial. Therefore the difference in mortality in this report might not be clinically

important, and a prospective randomized trial is required before cardiac surgeons adopt this therapy for this indication. The present post-hoc analysis raises the hypothesis that pexelizumab decreases early and 6-month mortality after combined AVR and CABG surgery. The effect of pexelizumab could be related to a decrease in the extent of myocardial ischemic injury and inhibition of inflammation cascades, leading to end-organ damage with the use of CPB in patients undergoing combined AVR and CABG. Further studies are needed to confirm this effect of the anti-C5 antibody pexelizumab.

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