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

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 CABG[5] 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.

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

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 $mg \cdot kg^{-1} \cdot h^{-1}$ 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 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