A phase 2 prospective, randomized, double-blind trial comparing the effects of tranexamic acid with ecallantide on blood loss from high-risk cardiac surgery with cardiopulmonary bypass (CONSERV-2 Trial)

Paula M. Bokesch, MD,[a,b] Gabor Szabo, MD,[c] Ryszard Wojdyga, MD,[d] Hilary P. Grocott, MD, FRCPC,[e] Peter K. Smith, MD,[f] C. David Mazer, MD, FRCPC,[g] Santosh Vetticaden, MD, PhD,[a] Alistair Wheeler, MD,[a] and Jerrold H. Levy, MD, FAHA[h]

Objective: Ecallantide is a recombinant peptide in the same class as aprotinin that inhibits plasma kallikrein, a major component of the contact coagulation and inflammatory cascades. Therefore, ecallantide was expected to reduce blood loss associated with cardiac surgery requiring cardiopulmonary bypass.

Methods: This prospective multinational, randomized, double-blind trial enrolled patients undergoing cardiac surgery using cardiopulmonary bypass for procedures associated with a high risk of bleeding. Patients were randomly assigned to ecallantide (n = 109) or tranexamic acid (high dose, n = 24; low dose, n = 85). Efficacy was assessed from the volume of packed red blood cells administered within the first 12 hours after surgery.

Results: The study was terminated early after the independent data safety and monitoring board observed a statistically significantly higher 30-day mortality in the ecallantide group (12%) than in the tranexamic acid groups (4%, $P = .041$). Patients receiving ecallantide received more packed red blood cells within 12 hours of surgery than tranexamic acid-treated patients: median = 900 mL (95% confidence interval, 600–1070) versus 300 mL (95% confidence interval, 0–523) ($P < .001$). Similar differences were seen at 24 hours and at discharge. Patients treated with the higher tranexamic acid dose received less packed red blood cells, 0 mL (95% confidence interval, 280–600), than the group treated with the lower dose, 400 mL (95% confidence interval, 0–400) ($P = .008$). No deaths occurred in the higher dose tranexamic acid group.

Conclusions: Ecallantide was less effective at reducing perioperative blood loss than tranexamic acid. High-dose tranexamic acid was more effective than the low dose in reducing blood loss. (J Thorac Cardiovasc Surg 2012;143:1022-9)

Excessive postoperative bleeding after cardiac surgery complicates conditions in 0.6% to 11% of patients undergoing procedures requiring cardiopulmonary bypass (CPB).[1] Hemorrhage and reoperation for bleeding significantly increase hospital length of stay and cost of care.[2,3] Transfusion of allogeneic blood products exposes patients to risks of transfusion-related adverse effects.[4]

The mechanism of bleeding from CPB is multifactorial. Contact activation of blood during CPB converts prekallikrein to kallikrein, plasminogen to plasmin, and prothrombin to thrombin, activating the coagulation cascade, fibrinolysis, and complement system and causing bleeding and a systemic inflammatory response.[5-8] The antifibrinolytics, aprotinin and tranexamic acid, are reported to decrease blood loss and transfusion requirements after CPB.[9,10] Aprotinin has also been reported to modulate the systemic inflammatory response and platelet dysfunction mediated by kallikrein, thrombin, and plasmin.[11] Although both

From Cubist Pharmaceuticals, Inc,[a] Lexington, Mass; St Elizabeth's Hospital, Tufts University School of Medicine,[b] Boston, Mass; University of Heidelberg,[c] Heidelberg, Germany; Institute of Cardiology,[d] Warsaw, Poland; University of Manitoba, Winnipeg,[e] Manitoba, Canada; Duke University Medical Center,[f] Durham, NC; University of Toronto, St Michael's Hospital,[g] Toronto, Ontario, Canada; and Emory University School of Medicine,[h] Atlanta, Ga.

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Address for reprints: Paula M. Bokesch, MD, Cubist Pharmaceuticals, Inc. 65 Hayden Avenue, Lexington, MA 02421 (E-mail: paula.bokesch@cubist.com).

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Abbreviations and Acronyms

ACT = activated clotting time
BART = Blood Conservation Using Antifibrinolytics in a Randomized Trial
CABG = coronary artery bypass graft
CPB = cardiopulmonary bypass
DSMB = Data Safety Monitoring Board
FFP = fresh-frozen plasma
MI = myocardial infarction
PRBC = packed red blood cell
WBHC = whole blood heparin concentration

aprotinin and tranexamic acid have been shown to reduce perioperative blood loss and the need for blood transfusion after CPB, aprotinin was used more widely in cardiac surgery with a high risk for bleeding.[12] However, aprotinin was recently withdrawn from marketing because of safety concerns, consequently decreasing the therapeutic options available to attenuate blood loss in high-risk cardiac surgery.

Ecallantide is a novel, recombinant human peptide derived from the first Kunitz domain of the human tissue factor pathway inhibitor-1 that inhibits the tissue factor pathway of coagulation.[13] Ecallantide has a high affinity and specificity for human plasma kallikrein, a key enzyme in contact activation of the coagulation cascade and complement activation of the inflammatory cascade.[13] Ecallantide and aprotinin are of the same class of drugs known as Kunitz protease inhibitors that have been shown in animal models to reduce post-CPB blood loss.[14] Aprotinin is a broad-spectrum protease inhibitor [15] and a more potent plasmin inhibitor than ecallantide, which is desirable during CPB to decrease fibrinolysis but less desirable postoperatively and, in theory, may contribute to the thrombotic complications associated with aprotinin.[16,17] Aprotinin is derived from animal protein, making it immunogenic, whereas ecallantide is recombinant, derived from human protein with less potential for antigenicity.[15]

Ecallantide's ability to attenuate the inflammatory response during CPB and to decrease consumption of coagulation factors during CPB and bradykinin-mediated capillary leak support its investigation in cardiac surgery.[18] Two pilot studies in 111 patients undergoing cardiac operations with CPB for primary coronary artery bypass grafting (CABG) or single-valve surgery demonstrated ecallantide safety and decreased perioperative transfusion of blood products.[19] Ecallantide was recently approved for marketing by the US Food and Drug Administration for treatment of hereditary angioedema, supporting its anti-inflammatory mechanism of action.

We describe the results of a phase 2 clinical trial designed to evaluate the relative efficacy and safety of ecallantide compared with tranexamic acid to reduce blood loss in patients undergoing cardiac surgery using CPB for operations associated with a high risk of bleeding.

MATERIALS AND METHODS

Study Design

This prospective, double-blind, randomized phase 2 trial was conducted at 36 centers in 3 countries (Germany, 20 sites; Poland, 15 sites; and United States, 1 site) between March and December 2009. The protocol was approved by the institutional review board of each study center, and all patients or legally authorized representatives provided written consent. The study was designed jointly by Cubist Pharmaceuticals (Lexington, Mass) and the investigators. Data were collected by the investigators and monitored by a third-party contract research organization (Global Research Services, Rockville, Md). Data analyses and biostatistics were performed by an independent third party (InVentiv Clinical, Hunt Valley, Md). All authors had full access to the data.

Patients

Eligible patients included men or women aged 18 years or more and 85 years or less undergoing cardiac surgery using CPB for one of the following operations associated with a higher risk of bleeding: repeat sternotomy, surgery to repair or replace more than 1 valve, or combined CABG plus repair or replacement of at least 1 valve. Exclusion criteria were any off-pump procedure; planned blood transfusion during the perioperative period; weight less than 55 kg; planned hypothermia (<28°C); pregnant or lactating women; ejection fraction less than 30%; myocardial infarction (MI) within 5 days of surgery; stroke or transient ischemic attack within 3 months before surgery; hypotension or heart failure requiring the use of inotropes or mechanical devices within 24 hours of surgery; creatinine greater than 2.0 mg/dL within 48 hours of surgery; preoperative hepatic enzymes more than 2.5 times the upper limit of normal; hematocrit less than 32%; platelet count below normal range at site laboratory; history of bleeding or clotting disorder; history of heparin-induced thrombocytopenia; prothrombin time or activated partial thromboplastin time more than 1.5 times the normal range unless receiving heparin; color blindness; evidence of acute thromboses or thromboembolism; and use of antiplatelet drugs or anticoagulants within prespecified times.

Baseline Data Collection and Randomization

Patients and all study personnel except the investigative pharmacist at each site were blinded to treatment assignment. Eligible patients were randomized 1:1 to ecallantide or tranexamic acid. All patients were centrally randomized using an interactive voice-response system and a computer-generated schedule. After consenting, screening assessments included medical and surgical history, physical examination, and laboratory tests.

Anesthesia and surgery were conducted according to each institution's standard of care. All patients were given the same fixed loading dose of heparin (300 U/kg) and pump priming dose (10,000 U). Additional heparin, up to 100 U/kg, was given as needed to achieve an activated clotting time (ACT) of more than 450 seconds. Because ecallantide may spuriously prolong the ACT, whole blood heparin concentration (WBHC) was monitored to ensure adequate anticoagulation and preserve blinding. Study medication was not given until an ACT of more than 450 seconds had been achieved, and the corresponding WBHC was the target concentration during CPB. If necessary, additional boluses of 3000 to 5000 units were given to maintain target heparin concentration while on CPB. WBHC was measured at a minimum of every 30 minutes.

To standardize transfusion practice across institutions and minimize variability that might confound study results, the protocol included the transfusion guidelines from The Society of Thoracic Surgeons Blood Conservation Guideline Task Force 2007.[20] The investigators were instructed