Journal of the American College of Cardiology
Vol. 61, No. 20, 2013

ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.03.003

Effects of the P-Selectin Antagonist Inclacumab on Myocardial Damage After Percutaneous Coronary Intervention for Non–ST-Segment Elevation Myocardial Infarction

Results of the SELECT-ACS Trial

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Objectives The study aimed to evaluate inclacumab for the reduction of myocardial damage during a percutaneous coronary intervention (PCI) in patients with non–ST-segment elevation myocardial infarction.

Background P-selectin is an adhesion molecule involved in interactions between endothelial cells, platelets, and leukocytes. Inclacumab is a recombinant monoclonal antibody against P-selectin, with potential anti-inflammatory, antithrombotic, and antiatherogenic properties.

Methods Patients (N = 544) with non–ST-segment elevation myocardial infarction scheduled for coronary angiography and possible ad hoc PCI were randomized to receive 1 pre-procedural infusion of inclacumab 5 or 20 mg/kg or placebo. The primary endpoint, evaluated in patients who underwent PCI, received study medication, and had available efficacy data (n = 322), was the change in troponin I from baseline at 16 and 24 h after PCI.

Results There was no effect of inclacumab 5 mg/kg. Placebo-adjusted geometric mean percent changes in troponin I with inclacumab 20 mg/kg were −24.4% at 24 h ($p = 0.05$) and −22.4% at 16 h ($p = 0.07$). Peak troponin I was reduced by 23.8% ($p = 0.05$) and area under the curve over 24 h by 33.9% ($p = 0.08$). Creatine kinase-myocardial band yielded similar results, with changes of −17.4% at 24 h ($p = 0.06$) and −16.3% at 16 h ($p = 0.09$). The incidence of creatine kinase-myocardial band increases >3 times the upper limit of normal within 24 h was 18.3% and 8.9% in the placebo and inclacumab 20-mg/kg groups, respectively ($p = 0.05$). Placebo-adjusted changes in soluble P-selectin level were −9.5% ($p = 0.25$) and −22.0% ($p < 0.01$) with inclacumab 5 and 20 mg/kg. There was no significant difference in adverse events between groups.

Conclusions Inclacumab appears to reduce myocardial damage after PCI in patients with non–ST-segment elevation myocardial infarction. (A Study of RO4905417 in Patients With Non ST-Elevation Myocardial Infarction [Non-STEMI] Undergoing Percutaneous Coronary Intervention; NCT01327183) (J Am Coll Cardiol 2013;61:2048–55) © 2013 by the American College of Cardiology Foundation

Percutaneous coronary intervention (PCI) is a widely used revascularization procedure for patients with stable and unstable coronary artery disease, but varying degrees of periprocedural myocardial damage (often relatively minor) occurs in as many as 50% of patients, even after a seemingly

See page 2056

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uneventful PCI (1–3). Although the pathophysiology of post-PCI myocardial damage is multifactorial, inflammation and platelet activation appear to play pivotal roles (4–7). P-selectin, a cell adhesion molecule expressed on activated endothelial cells and platelets, plays a critical role in leukocyte tethering and rolling on the vessel wall and subsequent diapedesis through interactions with P-selectin glycoprotein ligand 1 (8). It also promotes platelet rolling and adhesion to the activated vessel wall. When expressed on the cell surface, P-selectin therefore affects both the inflammatory and thrombotic cascades, induces formation of procoagulant microparticles, and mediates microparticle and leukocyte recruitment to thrombi, which collectively promotes both leukocyte recruitment to activated endothelium and thrombus growth and stabilization (9). Studies in mice, rats, and pigs have suggested that inhibition of P-selectin with either an anti–P-selectin monoclonal antibody or P-selectin glycoprotein ligand 1–immunoglobulin complex can significantly decrease neutrophil and platelet adhesion, macrophage accumulation, and neointimal formation after arterial injury (10–13). Inclacumab is a highly specific human recombinant monoclonal antibody against P-selectin, which has been shown to reduce CD11b expression (known to increase after PCI [14]) on neutrophils in a concentration-dependent fashion (data on file, F. Hoffmann-La Roche). The SELECT-ACS (Effects of the P-Selectin Antagonist Inclacumab on Myocardial Damage After Percutaneous Coronary Intervention for Non-ST-Elevation Myocardial Infarction) clinical trial was designed to determine the efficacy of inclacumab in reducing myocardial damage during PCI in patients with non–ST-segment elevation myocardial infarction (NSTEMI). We hypothesized that inclacumab would reduce myocardial damage through the effects of P-selectin inhibition on both the inflammatory and thrombotic cascades.

Methods

Study design and procedures. This prospective, international, multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of inclacumab (RO4905417, F. Hoffmann-La Roche) in patients with NSTEMI scheduled for coronary angiography and PCI. The study was coordinated by the Montreal Heart Institute Coordinating Center. Patients reviewed and signed an informed consent form approved by the institutional review boards of the study sites before any study-related procedures. Patient screening was performed up to 3 days before PCI, followed by treatment involving a single infusion of inclacumab (5 or 20 mg/kg) or placebo before PCI. Patients were monitored for 24 h for efficacy and 120 days for safety evaluations (Fig. 1). Troponin I (TnI) and creatine kinase-myocardial band (CK-MB) levels were measured in a central laboratory.

Abbreviations and Acronyms

ANCOVA = analysis of covariance
AUC = area under the curve
CK-MB = creatine kinase-myocardial band
NSTEMI = non–ST-segment elevation myocardial infarction
PCI = percutaneous coronary intervention
TnI = troponin I

The study drug was administered between 1 and 24 h before PCI over a 1-h infusion period. Patients were randomized in a 1:1:1 ratio to 3 treatment arms: inclacumab 5 mg/kg, inclacumab 20 mg/kg, or placebo. A stratified randomization was used to account for the presence or absence of known diabetes to ensure equal distribution within the randomized groups. A randomization schedule was generated using SAS statistical software version 9.3 (SAS Institute, Cary, North Carolina). Patients received concomitant evidence-based therapies as currently recommended by the American College of Cardiology/American Heart Association guidelines. This included the administration of aspirin, a P2Y12 inhibitor, lipid-lowering medications (preferably a statin), and a renin-angiotensin system inhibitor as deemed necessary by the investigator. Patients were assessed at baseline and at 8, 16, and 24 h post-PCI or at the time of discharge if patients were discharged before the last time point. All patients returned 30 and 120 days post-infusion for follow-up safety visits that included the assessment of adverse events, routine clinical laboratory tests, physical examination, and electrocardiograms. A subset of the enrolled patients (n = 177) willing to participate in an optional substudy had additional blood samples collected at baseline and at 8 h post-PCI for the measurement of plasma-soluble P-selectin levels using a specific enzyme-linked immunosorbent assay (R&D Systems Inc., Minneapolis, Minnesota).

Study population. A total of 544 patients at 66 centers located in Canada, the United States, Poland, and the Netherlands were enrolled in this study. Patients were included in the study if they were between 18 and 85 years old, were diagnosed with NSTEMI as defined by the American College of Cardiology/American Heart Association guidelines, and scheduled for coronary angiography and possible ad hoc PCI. Reasons for exclusion were PCI within the past 72 h; recent thrombolytic therapy; recent cerebrovascular disease or stroke; bleeding disorders; significant blood dyscrasia; severe uncontrolled hypertension; previous coronary artery bypass graft surgery; active or recent chronic bacterial, parasitic, or viral infection; uncontrolled diabetes mellitus; intercurrent infection; severe renal failure; hepatic failure; severe active inflammatory or immune-mediated disease; pregnancy or planned pregnancy; or any other condition or disease that would render the patient unsuitable for the study in the opinion of the investigator. Patients

investigator for a past Roche-sponsored trial. Dr. Tanguay is a consultant to Roche. Dr. Wright is a research consultant to Roche/Genentech, 3M, and Sanofi Regeneron, and is a consultant to Gilead. Dr. Ibrahim is a proctor and consultant for St. Jude and Gore. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 22, 2013; revised manuscript received February 28, 2013, accepted March 2, 2013.