ABSTRACT

Background: Abciximab has been found to reduce major adverse cardiovascular events in patients with acute coronary syndrome (ACS). A previous study reported on the tolerability of biogeneric abciximab in patients with ACS. This formulation has been approved by the Korea Food and Drug Administration and is currently being marketed. Its ex vivo antiplatelet effect, however, has not been compared with that of branded abciximab.

Objective: The purpose of the present study was to compare ex vivo antiplatelet activity, angiographic outcome, and bleeding complications between biogeneric and branded abciximab.

Methods: This prospective, open-label, randomized, controlled study was conducted in Korea. Patients with ACS who underwent percutaneous coronary intervention (PCI) were randomized to receive biogeneric abciximab or branded abciximab. All patients received intracoronary unfractionated heparin 70 IU/kg and either biogeneric or branded abciximab 0.25 mg/kg IV bolus ~10 minutes before undergoing PCI, followed by a 0.125 μg/kg/min 12-hour infusion of the same formulation. The antiplatelet effect of both drugs was assessed at 3 time points (at baseline, and 10 minutes and 24 hours after the end of the bolus infusion) using a validated rapid platelet-function assay.

Results: In total, 37 patients (30 men and 7 women; 19 receiving biogeneric abciximab and 18 receiving branded abciximab) were included. Patient demographics did not differ significantly between the 2 groups (16 men [84.2%] and 3 women [15.8%] in the biogeneric group vs 14 men [77.8%] and 4 women [22.2%] in the branded group; mean [SD] age, 65 [11] vs 60 [10] years; weight, 64.6 [8.7] vs 67.9 [10.1] kg, respectively). The bolus and the continuous infusion of the biogeneric and branded formulations achieved similar levels of platelet inhibition, with a mean (SD) inhibition of platelet aggregation >90% at 10 minutes after the end of the bolus infusion (94.7% [8.2%] vs 92.6% [16.9%], respectively; \( P = NS \)) and >65% at 24 hours (68.1% [9.8%] vs 70.9% [9.7%]; \( P = NS \)) compared with baseline. One thrombolysis in myocardial infarction major bleeding complication (retroperitoneal hemorrhage) was reported in a patient who received biogeneric abciximab.

Conclusion: There were no statistically significant differences in the antiplatelet effects of these 2 formulations in this small, selected population of Korean patients with ACS. (Clin Ther. 2009;31:1804–1811) © 2009 Excerpta Medica Inc.

Key words: acute coronary syndrome, abciximab, platelet aggregation.

INTRODUCTION

Platelet aggregation is pivotal in the pathogenesis of acute coronary syndrome (ACS) and in the occurrence of complications after percutaneous coronary intervention (PCI).\(^1\) In a randomized, controlled trial comparing abciximab and placebo in patients (\( N = 2022 \)) with ACS undergoing PCI, the frequency of adverse events was lower in those who received abciximab than in the control, and clinical benefits were maintained at 1 year after administration.\(^2\) However, the economic cost associated with abciximab has hindered its use in developing countries.
Biogenerics are generic versions of biotechnology-based drugs (biopharmaceuticals or biologics), such as insulin and human growth hormone, which essentially are large protein molecules derived from living cells. The biogeneric abciximab is an antibody of the glycoprotein IIb/IIIa receptor. It achieved economic merit by renovating the cell culture system. In the cell culture process, a fed-batch process using a disposable bioreactor is introduced, and the use of disposable components reduces the complexity of validation. A single-use, disposable bioreactor offers many advantages in the manufacturing of biologics. Because a single-use bag is clean and ready to use, sterilization and cleaning are not needed, which eliminates the chance of cross-contamination between process runs. A previous multicenter, randomized, open-label, clinical trial found that biogeneric abciximab was well tolerated in patients with ACS undergoing PCI. However, ex vivo antiplatelet activity was not directly compared with that of branded abciximab.

The purpose of this pilot study was to compare ex vivo antiplatelet activity, angiographic outcome, and bleeding complications between biogeneric and branded abciximab.

**PATIENTS AND METHODS**

**Inclusion and Exclusion Criteria**

Patients aged 18 to 80 years with a diagnosis of ACS who underwent PCI between October 2007 and June 2008 at the Cardiovascular Center at Seoul National University Hospital in Seoul, Korea, were eligible. Patients were excluded if they were aged >80 years, pregnant, or had bleeding tendencies, a history of cerebrovascular accident within the previous 2 years, a platelet count <120,000/μL, or major surgery within 6 weeks of the study.

**Study Design**

This prospective, open-label, randomized, controlled study was conducted in Korea. Eligible patients were prospectively randomized to receive biogeneric or branded abciximab. Randomization was achieved using a random numbers table. An arbitrary sample size of 18 patients per group was selected for this pilot study. All patients received intracoronary unfractionated heparin 70 IU/kg and either biogeneric or branded abciximab 0.25 mg/kg IV bolus ~10 minutes before undergoing PCI. Intravenous lines were flushed after the bolus injection. Patients then received a 0.125 μg/kg/min infusion (biogeneric or branded as assigned) dissolved in 0.9% sterile saline or 5.0% dextrose for 12 hours. After completion of the PCI, patients were observed in the cardiovascular unit of the hospital for vital sign monitoring and bleeding complications over a period of 24 hours.

The study protocol was approved by the institutional review board and ethics committee of Seoul National University Hospital. Written informed consent was obtained from patients before enrollment. For patients who were unconscious, family members provided consent.

**Blood Collection and Analysis**

Blood samples were collected at baseline, and 10 minutes and 24 hours after the end of the bolus infusion to assess antiplatelet function (antiplatelet inhibition). At each time point, 20 mL of blood was collected in 3.2% sodium citrate tubes and maintained at a room temperature of 20°C (68°F) to 25°C (77°F). Blood samples for baseline analysis were collected from a radial or femoral artery catheter introducer sheath, a device used for access and bloodless exchange of guidewires and catheters, inserted into the side of the arm. Blood samples for the 10-minute postinfusion analysis were collected via guiding catheter, a specialty catheter designed for balloon-stent catheter delivery, after ≥10 mL of blood was drawn from the guiding catheter with a 12-mL syringe and discarded. Blood samples drawn at the 24-hour time point were collected from the antecubital vein using a 22-gauge BD Vacutainer Eclipse blood collection needle with a preattached holder (BD Diagnostics, Franklin Lakes, New Jersey).

To the best of our knowledge, there are no data indicating that site (blood collection location) and method of collection have effects on platelet activity. In the present study, all blood collection sites and methods were consistent. Therefore, it was assumed that collecting blood from different locations (but the same in each patient at each time point) would not pose a threat to the validity of the results.

**Rapid Platelet-Function Analysis**

The Ultegra rapid platelet-function assay (RPFA) is an automated turbidimetric whole-blood assay de-
signed to assess platelet function based on the ability of activated platelets to bind to fibrinogen (Accu-metrics, Inc., San Diego, California). To initiate platelet activation without producing fibrin formation, thrombin receptor-activating peptide is incorporated into the assay.

**Glycoprotein IIb/IIIa Assay**

The VerifyNow GP IIb/IIIa (Accumetrics) is a device that measures the interaction between platelet glycoprotein (GP) IIb/IIIa receptors and fibrinogen-coated polystyrene beads, leading to agglutination of the beads. Blockade of GP IIb/IIIa receptors by abciximab interferes with this interaction, thereby reducing the agglutination. The VerifyNow GP IIb/IIIa measures this change in optical signal and reports results in platelet aggregation units (PAU).

**Primary End Point**

The primary end point was the antiplatelet effect of both drugs assessed via RPFA. Platelet aggregation inhibition was measured using the VerifyNow GP IIb/IIIa kit at the 3 time points (baseline [before PCI] and 10 minutes and 24 hours after the bolus infusion). The assays were conducted by investigators blinded to treatments.

**Secondary End Points**

The secondary end point was angiographic outcome after PCI, based on thrombolysis in myocardial infarction (TIMI) flow grade, a 4-point scoring system, with scores ranging from 0 to 3 (0 = no perfusion; 1 = penetration without perfusion; 2 = partial reperfusion; 3 = complete perfusion), referring to levels of coronary blood flow assessed during PCI. The frequency of major bleeding complications was also a secondary end point. TIMI major bleeding complications were defined as overt, clinical bleeding (or documented intracranial or retroperitoneal hemorrhage) associated with a decrease >5 g/dL of the blood hemoglobin level or >15% of the hematocrit. The analyses were evaluated by personnel unblinded to treatment and who did not pose any conflicts of interest.

**Statistical Analysis**

Data are expressed as mean (SD) or as number (%). Continuous variables were compared using the t test (between-group comparisons); categoric variables were compared using the χ² test. All statistical analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, Illinois), and a P value <0.05 was considered statistically significant. Because this was a pilot study, a sample size calculation was not required and therefore was not performed.

**RESULTS**

**Patients**

There were a total of 388 patients with ACS who underwent PCI during the study period (October 2007–June 2008). However, 351 patients refused enrollment. Therefore, 37 patients (30 men and 7 women; 19 receiving biogeneric abciximab and 18 receiving branded abciximab) were included (Figure 1).

Baseline demographic characteristics did not differ significantly between the 2 groups (16 men [84.2%] and 3 women [15.8%] in the biogeneric group vs 14 men [77.8%] and 4 women [22.2%] in the branded group; mean [SD] age, 65 [11] vs 60 [10] years; weight, 64.6 [8.7] vs 67.9 [10.1] kg, respectively). The table shows baseline demographic and clinical characteristics. There were no significant between-group differences.

**Primary End Point**

**Inhibition of Platelet Function**

Ten minutes and 24 hours after administration of the bolus dose of abciximab, there was no significant reduction in the mean PAU from baseline (baseline: mean [SD] 207.7 [48.2] vs 206.5 [44.9], P = NS; 10 minutes: 12.2 [18.9] vs 15.4 [33.2], P = NS; and 24 hours: 69.8 [23.0] vs 57.1 [16.4], P = NS) (Figure 2). The bolus and the following continuous infusion of the biogeneric and branded formulations achieved similar levels of platelet inhibition, with a mean inhibition of platelet aggregation >90% at 10 minutes after the end of bolus infusion (94.7% [8.2%] vs 92.6% [16.9%], respectively; P = NS) and >65% at 24 hours (68.1% [9.8%] vs 70.9% [9.7%]; P = NS) compared with baseline (Figure 3). A blunted antiplatelet response (134 PAU at 10 minutes and 69 PAU at 24 hours, Figure 4) was observed in 1 patient who received branded abciximab. The exact mechanism of the blunted response was not fully understood.

**Secondary End Points**

Before PCI, 4 patients had TIMI grade 0 or 1 flow (TIMI grade 0 flow, 3 [biogeneric] and TIMI grade 1 flow, 1 [branded]). All patients achieved TIMI grade 3 flow after PCI.
Figure 1. Flow of patients throughout the study period. ACS = acute coronary syndrome; PCI = percutaneous coronary intervention.

Table. Baseline demographic and clinical characteristics of patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI) with biogeneric or branded abciximab 12-hour infusion.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Biogeneric† (n = 19)</th>
<th>Branded‡ (n = 18)</th>
<th>Variable</th>
<th>Biogeneric† (n = 19)</th>
<th>Branded‡ (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, no. (%)</td>
<td></td>
<td></td>
<td>Comorbidity, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (84.2)</td>
<td>14 (77.8)</td>
<td>NSTEMI</td>
<td>12 (63.2)</td>
<td>10 (55.6)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (15.8)</td>
<td>4 (22.2)</td>
<td>STEMI</td>
<td>1 (5.3)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>65 (11)</td>
<td>60 (10)</td>
<td>Multivessel disease</td>
<td>7 (36.8)</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>64.6 (8.7)</td>
<td>67.9 (10.1)</td>
<td>Thrombus</td>
<td>7 (36.8)</td>
<td>9 (50.0)</td>
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<tr>
<td>Comorbidity, no. (%)</td>
<td></td>
<td></td>
<td>Platelet count × 103/μL, mean (SD)</td>
<td>212.1 (55.7)</td>
<td>211.2 (46.2)</td>
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<td>Diabetes mellitus</td>
<td>11 (57.9)</td>
<td>6 (33.3)</td>
<td>TIMI flow grade 0 or 1 before PCI</td>
<td>3 (10.5)</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (63.2)</td>
<td>13 (72.2)</td>
<td>TIMI flow grade 3 after PCI</td>
<td>19 (100)</td>
<td>18 (100)</td>
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<tr>
<td>Smoker§</td>
<td>13 (68.4)</td>
<td>11 (61.1)</td>
<td>Number of stents, mean (SD)</td>
<td>1.89 (1.2)</td>
<td>1.50 (0.7)</td>
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<tr>
<td>Dyslipidemia</td>
<td>10 (52.6)</td>
<td>8 (44.4)</td>
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<tr>
<td>Previous CABG</td>
<td>1 (5.3)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>6 (31.6)</td>
<td>5 (27.8)</td>
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</tr>
</tbody>
</table>

CABG = coronary artery bypass graft; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TIMI = thrombolysis in myocardial infarction.

*There were no significant between-group differences.
† Trademark: Clotinab® (ISU ABXIS Co., Ltd., Seoul, Korea).
‡ Trademark: ReoPro® (Lilly Korea, Seoul, Korea).
§ Active smokers as well as ex-smokers who stopped <1 year before enrollment.
Figure 2. Mean platelet aggregation units (PAU) in patients receiving either biogeneric or branded abciximab. There were no significant between-group differences. *Trademark: Clotinab® (ISU ABXIS Co., Ltd., Seoul, Korea); †Trademark: ReoPro® (Lilly Korea, Seoul, Korea).

Figure 3. Mean (SD) percent inhibition of platelet aggregation. The bolus and the following continuous infusion of biogeneric versus branded abciximab resulted in inhibition >90% at 10 minutes (94.7% [8.2%] vs 92.6% [16.9%], respectively) and >65% at 24 hours (68.1% [9.8%] vs 70.9% [9.7%]) compared with baseline. *Trademark: Clotinab® (ISU ABXIS Co., Ltd., Seoul, Korea); †Trademark: ReoPro® (Lilly Korea, Seoul, Korea).
DISCUSSION

As previously indicated, biogenerics are generic forms of biopharmaceuticals—molecules developed using biological processes, typically through modern biotechnology activity. In this study, the biogeneric abciximab

One patient (biogeneric) experienced a TIMI major bleeding complication (retroperitoneal bleeding), because of an arteriovenous fistula of the femoral puncture site. The patient underwent coil embolization of the fistula tract. No other TIMI major bleeding complication was reported.
mab had similar ex vivo antiplatelet effects, angiographic outcomes, and tolerability compared with branded abciximab in these patients with ACS. This finding is consistent with a previous report that found comparable tolerability of biogeneric abciximab with the branded drug.4 In the present study, 1 patient experienced a TIMI major bleeding complication (retroperitoneal bleeding) due to an arteriovenous fistula of the femoral puncture site. The patient underwent coil embolization of the fistula tract. However, there were no other TIMI major bleeding complications reported.

The efficacy of GP IIb/IIIa inhibitors has been reported in several clinical trials.2,9–14 The use of GP IIb/IIIa inhibitors has become a standard adjunctive pharmacotherapeutic intervention for PCI in high-risk patients. The American College of Cardiology/American Heart Association recommends the use of GP IIb/IIIa inhibitors in patients with unstable angina or non-ST elevation myocardial infarction undergoing PCI.15 However, the rate of GP IIb/IIIa inhibitor use in Korea is very low compared with Western countries.16,17 Because of the cost of the GP IIb/IIIa inhibitor, strict regulation by the medical insurance system limits its use in Korea.

Limitations
Although to our knowledge (based on a literature search of the MEDLINE database for English-language articles published between January 2005 and July 2009, and using the terms abciximab, Clotinab, glycoprotein IIb/IIIa, ISU301, and antiplatelet effects), this is the first pilot study to report the comparable antiplatelet effects of biogeneric and branded abciximab, the open-label design and small sample size limit our ability to draw definitive conclusions. Additionally, because this was a pilot study, a sample size calculation was not performed. Large, head-to-head comparative, randomized, double-blind trials are warranted to compare the antiplatelet effects of these 2 formulations of abciximab.

CONCLUSION
There were no statistically significant differences in the antiplatelet effects of these 2 formulations of abciximab in this small, selected population of Korean patients with ACS.

ACKNOWLEDGMENTS
The authors have indicated that they have no conflicts of interest regarding the content of this article.

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Address correspondence to: Hyo-Soo Kim, MD, PhD, Department of Internal Medicine, Seoul National University Hospital, 28 Yongdong-dong, Chongno-gu, Seoul 110–744, Korea. E-mail: hyosoo@snu.ac.kr