Abciximab Readministration

Results of the ReoPro Readministration Registry

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Background—Platelet glycoprotein IIb/IIIa blockade with abciximab (ReoPro) improves the clinical outcomes of percutaneous coronary intervention. This registry was conducted to characterize the effects of repeated administration of abciximab during intervention.

Methods and Results—We recruited 500 consecutive patients at 22 centers in the United States who were receiving abciximab for at least a second time during percutaneous coronary intervention. Safety was measured as the incidence of hypersensitivity reactions, major bleeding, and thrombocytopenia. Efficacy was assessed as event-free clinical success. Human antichimeric antibody (HACA) responses were also characterized. There were no cases of hypersensitivity (95% upper confidence bound, 0.3%), major bleeding, or death. Clinical success was 94.4%. Thrombocytopenia occurred in 23 patients (4.6%; 95% CI, 2.8% to 6.4%), including 12 (2.4%; 95% CI, 1.1% to 3.7%) who developed profound thrombocytopenia (<20×10⁹ cells/L). In 2 patients (0.4%), profound thrombocytopenia did not develop until after hospital discharge; in 4 (0.8%), profound thrombocytopenia recurred despite platelet transfusion. Before a first readministration, a positive HACA titer was present in 22 of 454 patients (4.8%); after a first readministration, an additional 82 of 432 (19.0%) became HACA-positive. HACA did not neutralize the in vitro inhibition of platelet aggregation by abciximab or correlate with clinical events.

Conclusions—The results, including overall rates of thrombocytopenia, were consistent with randomized clinical trials of first abciximab treatment. However, there was a shift from mild to profound thrombocytopenia, and cases of delayed presentation and of recurrent thrombocytopenia were seen. These findings suggest that indications and guidelines for first-time use apply to retreatment, particularly the systematic monitoring for thrombocytopenia. (Circulation. 2001; 104:870-875.)

Key Words: angioplasty • platelet aggregation inhibitors • pharmacodynamics • thrombocytopenia

Blockade of the platelet glycoprotein IIb/IIIa receptor during percutaneous coronary intervention (PCI) significantly reduces myocardial infarction, the need for urgent repeat intervention or coronary artery bypass surgery, and death.1–5 In addition, new indications are under investigation, including the medical treatment of non–ST-segment elevation acute coronary syndromes, facilitating conventional thrombolysis in acute ST-segment elevation myocardial infarction,7,8 and as adjunctive therapy in cerebrovascular disease and peripheral vascular intervention. Because atherosclerosis is a chronic process punctuated by brief episodes of high acuity, a substantial proportion of patients will likely require multiple courses of treatment with these agents well after an initial episode of care.

Abciximab (ReoPro), a chimeric (murine/human) monoclonal antibody fragment (c7E3 Fab), was the first glycoprotein IIb/IIIa antagonist to be approved and marketed.9,10 Because abciximab can induce an antibody response, concerns have been raised about the potential for anaphylaxis, thrombocytopenia, and reduced efficacy with repeated administration.11 Case series have reported that the readministration of abciximab is safe and effective.12 However, these
studies were small and underpowered. To evaluate abciximab readministration prospectively, we established the ReoPro Readministration Registry to determine its safety and efficacy and to evaluate the human antichimeric antibody (HACA) response of patients being retreated with abciximab.

Methods

The ReoPro Readministration Registry was a prospective, phase IV, multicenter registry initiated in March 1997. By August 1998, 500 patients had been recruited from 22 centers in the United States. All patients being treated with abciximab at least 7 days after a previous treatment were eligible for participation. The respective institutions enrolled consecutive, eligible patients. Informed consent was obtained from all patients who participated. The protocol was approved by the Institutional Review Boards of the participating centers (Appendix).

All patients received heparin and aspirin. PCI was performed per local standards. For a case to be a clinical success, PCI had to be performed (4 patients were enrolled and received abciximab but did not undergo PCI) and be defined as an angiographically successful procedure (with all target lesions reduced to a final visual stenosis <50%), without any major adverse cardiac events (death, myocardial infarction, or repeat urgent percutaneous intervention or surgical revascularization). The period of clinical follow-up was from the time of enrollment until hospital discharge. Patients were also observed for measures of safety, including bleeding, transfusion, allergic or anaphylactic reactions, and thrombocytopenia. Platelet counts were routinely obtained 4 hours after the abciximab bolus, the morning after the procedure, at 4 weeks, and as clinically indicated. Study data were collected prospectively on case report forms specifically designed for the Registry and were then entered into the Registry database.

Statistical Considerations

A sample size of 500 patients was calculated to provide a 95% confidence interval around a point estimate of the incidence of hypersensitivity reactions of ~1%. Events were tallied as reported by the Investigators on case report forms. Data are presented using simple descriptive statistics for continuous variables, and Fisher’s exact test was used to analyze categorical data. Baseline clinical and procedural variables were entered into a multivariable logistic regression model to determine predictors of thrombocytopenia and a HACA response.

Adjudication of Thrombocytopenia

Patients developing thrombocytopenia underwent further laboratory evaluation and independent adjudication of the probable cause. The diagnosis of thrombocytopenia induced by abciximab required a decrease in platelet count to <100×10^9 cells/L, with a fall >25% from baseline and the exclusion of pseudothrombocytopenia and heparin-induced thrombocytopenia as the cause. A diagnosis of heparin-induced thrombocytopenia was entertained in cases meeting the criteria of Poupland and colleagues, if heparin-dependent platelet-reactive antibodies were demonstrated using the C-serotonin release assay, or if increased levels of anti-heparin/PF4 antibodies were found by ELISA assay.

Immune Response Analysis

Blood specimens (to assay for the presence of HACA) were obtained at baseline before abciximab readministration, at 3 to 5 days or discharge (whichever came first), at 4 weeks, and at 8 weeks. Of note, the pre-exposure HACA titer before first abciximab administration could not be determined because a previous treatment with abciximab was a prerequisite to study entry. HACA response was characterized using a sandwich ELISA assay, as previously described. A serum sample was negative if the 1:50 diluted serum produced an ELISA optical density <0.4 or if neutralization results indicated anti-abciximab binding restricted to the cleaved Fab terminus. A neutralization result that indicated antibody binding to any other region of abciximab was positive for HACA. A serum neutralization result that did not localize antibody binding to the variable, constant, or Fab terminus regions of abciximab was designated as indeterminate.

Abciximab Neutralization Assay

Neutralization analyses were performed to determine whether HACA blocked the in vitro effects of abciximab. Both HACA-positive and HACA-negative serum samples (50 μL) were incubated with varying concentrations of abciximab for 10 minutes at 37°C to allow for the formation of abciximab-antibody complexes. The final concentrations of abciximab in the assays spanned the values of the drug attained in vivo (to the maximal theoretical in vivo concentration of 6.25 μg/mL). The mixtures were added to 450 μL of platelet-rich plasma (platelet count, 225±25×10^9 cells/L), and the samples were incubated an additional 5 minutes. The aggregation response to 10 μmol/L adenosine diphosphate for each sample was then determined. The level of inhibition of platelet aggregation was plotted against the concentration of abciximab. The concentration of abciximab that resulted in 50% inhibition of aggregation (IC50) was extrapolated by 4-parameter fit analysis, and the -fold difference in IC50 of abciximab in the presence of patient versus control sera was calculated.

Results

Patient Recruitment

A total of 23,436 patients undergoing PCI were screened to identify the 500 patients discussed in this report. Of the universe of patients screened, 10,118 (43.2%) were being treated with abciximab for the first time, whereas 500 (2.1%) were receiving abciximab for a second or greater time. Of these, 455 patients (91.0%) received abciximab for a second time (ie, a first readministration); the remaining 45 received abciximab for a third or greater time.

Safety

Of the 500 patients in the Registry, there were no cases of anaphylactic, allergic, or other hypersensitivity reactions (95% upper confidence bound, 0.3%). Bleeding (mostly minor) was reported in 13.0% of patients (65 of 500). Major bleeding events occurred in 8 patients (1.6%). All 8 required red blood cell transfusions; one also received platelets. There was no correlation between major bleeding and thrombocytopenia; 6 of the 8 patients with major bleeding had normal platelet counts, and only one patient with major bleeding had profound thrombocytopenia. The clinical expressions of major bleeding were 3 cases of pseudoaneurysm formation (2 required surgical repair), 2 cases of gross gastrointestinal bleeding, and 5 cases of gross genitourinary bleeding. There were no cases of retroperitoneal or intracranial hemorrhage.

All Thrombocytopenia

Thrombocytopenia, which was defined as a decline in platelet count to <100×10^9 cells/L with at least a decrease of 25% from baseline, developed in 4.6% of patients (23 of 500; 95% CI, 2.8% to 6.4%; Table). All cases of thrombocytopenia were adjudicated as being secondary to abciximab. No predictors of thrombocytopenia could be identified in multivariable regression modeling. The baseline HACA status was not predictive of the development of thrombocytopenia, nor was conversion from a negative HACA at baseline to a positive HACA at follow-up. By 4 weeks, platelet counts of
all patients with thrombocytopenia had returned to baseline levels.

In 16 of the 23 patients with thrombocytopenia, the characteristics were diagnostic of acute (within 24 hours) thrombocytopenia. Ten of these 16 patients developed a nadir platelet count, \(2 \times 10^9\) cells/L, 3 developed counts between 20 and \(5 \times 10^9\) cells/L, and 3 developed counts between 50 and \(100 \times 10^9\) cells/L. Of the remaining 7 (of 23) patients, the nadir in 3 developed between 24 and 48 hours; all 3 had nadir counts. \(50 \times 10^9\) cells/L. The other 4 (of 7) had normal platelet counts through hospital discharge or 48 hours (whichever came first) and developed thrombocytopenia (ranging from 11 to \(93 \times 10^9\) cells/L) after the 48-hour check. This included 2 patients who returned after discharge because of mucocutaneous bleeding who were found to have profound thrombocytopenia (Figure 1A). The characteristics of these last 4 cases suggested “delayed” or “late” abciximab-induced thrombocytopenia.

**Profound Thrombocytopenia**

Approximately half of the cases of thrombocytopenia (12 of 23, or 52%; incidence of 2.4%; 95% CI, 1.1% to 3.7%) were cases of profound thrombocytopenia (to a nadir platelet count <\(20 \times 10^9\) cells/L). These 12 patients (out of 23) received platelet transfusions. In 4 patients, the platelet count fell below \(20 \times 10^9\) cells/L at least one more time, necessitating repeat platelet transfusion after a first transfusion; 2 of these 4 patients ultimately required 4 separate platelet transfusions (Figure 1B). These patients experienced a >1 week resolution of thrombocytopenia. Of note, none of the 500 patients in the Registry, including those who developed thrombocytopenia, were known to have had thrombocytopenia after a previous abciximab treatment.

**Clinical Efficacy**

Clinical success was achieved in 94.4% of patients (468 of 496). There were no differences in success rates whether the patient was receiving a first readministration (94.7% clinical success; 428 of 452 patients) or a second or greater retreatment (90.9%; 40 of 44 patients; \(P=0.30\) between first and subsequent readministration). Analysis of clinical success by baseline HACA status showed that success was independent of baseline HACA status (96.3% clinical success with a positive HACA titer at baseline; 94.0% with a negative HACA titer at baseline; \(P=1.0\)).

The combined incidence of death, myocardial infarction, or emergency revascularization was 3.6% (18 of 500 patients). There were no deaths, but 5 patients (1.0%) developed abrupt closure, 16 (3.2%) sustained a myocardial infarction, 3 (0.6%) required urgent repeat PCI, and one (0.2%) underwent emergency coronary artery bypass graft surgery. The rate of clinical success was comparable or better than the same composite clinical end point observed in the abciximab

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**Rates of Thrombocytopenia by Baseline HACA Status in All Evaluable HACA Samples**

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>HACA-Negative</th>
<th>HACA-Positive</th>
<th>HACA Status Indeterminate</th>
<th>HACA Status Unknown</th>
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<tr>
<td>n</td>
<td>499</td>
<td>451</td>
<td>28</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>Nadir platelet count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;(100 \times 10^9) cells/L</td>
<td>23 (4.6)</td>
<td>18 (4.0)</td>
<td>2 (7.1)</td>
<td>1 (100.0)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>(\geq 50 \text{ but } &lt;100 \times 10^9) cells/L</td>
<td>7 (1.4)</td>
<td>7 (1.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>(\geq 20 \text{ but } &lt;50 \times 10^9) cells/L</td>
<td>4 (0.8)</td>
<td>3 (0.6)</td>
<td>1 (3.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>&lt;(20 \times 10^9) cells/L</td>
<td>12 (2.4)</td>
<td>8 (1.8)</td>
<td>1 (3.6)</td>
<td>1 (100.0)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>HACA status after abciximab readministration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Negative</td>
<td>309 (61.9)</td>
<td>297 (65.9)</td>
<td>2 (7.1)</td>
<td>0 (0.0)</td>
<td>10 (25.6)</td>
</tr>
<tr>
<td>Positive</td>
<td>110 (22.0)</td>
<td>85 (18.8)</td>
<td>22 (78.6)</td>
<td>0 (0.0)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>3 (0.6)</td>
<td>2 (0.4)</td>
<td>0 (0.0)</td>
<td>1 (100.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>77 (15.4)</td>
<td>67 (14.3)</td>
<td>4 (14.3)</td>
<td>0 (0.0)</td>
<td>6 (31.6)</td>
</tr>
</tbody>
</table>

Results are expressed as No. of patients (%).

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**Figure 1.** Time course and response to platelet transfusion of patients developing profound thrombocytopenia. A, Two patients developed delayed profound thrombocytopenia. Platelet counts remained normal for the first 24 hours (to patient discharge), and thrombocytopenia was detected several days later because of bleeding. B, Four patients redeveloped profound thrombocytopenia after receiving platelet transfusions for the treatment of profound thrombocytopenia; recovery from thrombocytopenia was also prolonged in these cases.
HACA did not neutralize abciximab. The two curves superimpose, indicating that patient positive for HACA at a titer of 1:100 vs serum from a control subject. The two curves superimpose, indicating that HACA neutralization of abciximab: individual sample treatment arm of the randomized trials of abciximab versus placebo in PCI (Figure 2).

HACA
The Table presents HACA titer data before and after readministration of abciximab. The aggregate data for all patients in the Registry with evaluable HACA data indicate the presence of HACA before readministration in 5.6% of patients (28 of 499; 95% CI, 3.6% to 7.6%). Before a first readministration, a positive HACA titer was present in 22 of 454 patients (4.8%; 95% CI, 2.8% to 6.8%). After a first readministration, an additional 82 of 432 patients (19.0%; 95% CI, 15.3% to 22.7%) who were initially HACA-negative became HACA-positive. Combining these latter patients with those positive at baseline, approximately one-quarter of patients were thus HACA positive after 2 exposures to abciximab. In multivariable regression modeling, the only variable predictive of the development of a positive HACA was increasing age (P=0.0116). For patients who developed a HACA response, the peak titer occurred 1 month after drug exposure.

Abciximab neutralization studies showed that HACA did not neutralize the anti-platelet activity of abciximab. Figure 3 shows a representative abciximab inhibition curve for a serum sample positive for HACA at a titer of 1:100. The graph illustrates that the abciximab inhibitory profiles with the nonhuman murine (mouse-derived) regions on monoclonal antibodies are known to elicit immune responses. For example, OKT3 (Orthoclone) has been associated with a human antimurine antibody response on first administration in 86% of patients; the diagnostic agent satumomab (OncoScint) is associated with development of human antimurine antibody in 55% of patients. The parent molecule of abciximab is a murine monoclonal IgG antibody to glycoprotein IIb/IIIa, 7E3. Concerns about the potential antigenicity of 7E3 led to molecular re-engineering that produced a smaller chimeric (human-mouse) antibody fragment c7E3 Fab, or abciximab. This Fab molecule consists of human-constant regions with murine-variable regions (from 7E3) on both the heavy and light chains. Even with these changes, ~6% to 7% of patients develop a HACA response after the first administration of abciximab. The HACA ELISA results both the HACA positive and control sera superimpose on one another. The -fold differences for the abciximab IC50 for the 27 HACA-positive analyzable samples are shown in Figure 4. The mean -fold difference in IC50 profiles for HACA titers ranging from 1:50 to 1:800 are highly consistent with the HACA negative sera value (n=25), indicating no diminution of the inhibition of in vitro platelet aggregation by abciximab. The only suggestion of neutralization was with serum from the one patient with a positive HACA titer of 1:3200.

Discussion
The observations of the ReoPro Readministration Registry document that the profile of abciximab retreatment remains concordant with the large randomized clinical trials of the first administration of abciximab. Key observations include the following: no cases suggesting a hypersensitivity reaction were identified, and rates of bleeding were low and consistent with reported clinical trial data and current clinical practice. Overall rates of thrombocytopenia were similar to those after first administration. However, the incidence of profound thrombocytopenia (platelet count <20×109 cells/L) was higher than that seen with first treatment. Clinical success remained high, consonant with outcomes reported in the literature, with major adverse cardiac events occurring only infrequently. Finally, the pharmacodynamic analyses showed that the dose response (with respect to platelet inhibition) remained unchanged in the presence or absence of HACA.
indicate that the anti-abciximab responses are predominantly of the IgG isotype, not the IgE antibodies associated with allergic reactions and anaphylaxis. HACA titers were generally low, developed within 2 to 4 weeks, and peaked between 4 and 8 weeks.

In the Registry, the presence (or absence) of HACA was not predictive of the presence (or absence) of adverse clinical events, bleeding, thrombocytopenia, or immune-mediated phenomena. HACA at titers <1:3200 also did not neutralize (or predict neutralization of) abciximab. Thus, determining the HACA titer before abciximab administration does not seem to have predictive clinical utility. This conclusion, however, must be tempered by the limited number of HACA-positive patients in this study.

In the randomized clinical trials of first-time administration of abciximab, the only drug-related phenomenon was thrombocytopenia (to a platelet count of <100×10⁹ cells/L) at a composite incidence of 3.5% in the abciximab arms of the respective trials. The only finding of clinical concern raised by this study was also thrombocytopenia. Note that in order to be eligible for the Registry, patients could not have developed thrombocytopenia after a previous treatment with abciximab. In other words, previous exposure without the development of thrombocytopenia did not preclude the development of thrombocytopenia on re-exposure. Thus, follow-up platelet counts need to be obtained whenever abciximab is given, whether as a first treatment or a re-exposure.

Profound thrombocytopenia (a rapid decline, usually within 24 hours, to a platelet count of <20×10⁹ cells/L) due to abciximab occurs in 0.5% to 1% of patients receiving abciximab for the first time. Although the mechanism is unclear, this disorder is thought to be due to clearance of platelets from circulation, mediated by native antibodies that recognize a bound glycoprotein IIb/IIIa inhibitor-platelet complex. Our data suggest that the incidence of this disorder is higher with readministration than with first-time administration. This higher incidence may be due to the persistence of antibodies that develop after first exposure, an anamnestic immunological response, or both. Thrombocytopenia may not have become clinically evident with first exposure because the residual drug concentration was below the per-platelet threshold required to accelerate platelet clearance by the time a sufficient titer of antibody had developed. Because the overall rate of all thrombocytopenia was not increased compared with previously reported rates, this represents a shift from mild to profound thrombocytopenia.

Two other observations warrant further elaboration. First, a delayed or late presentation (after hospital discharge, with the nadir identified between days 5 and 7) of thrombocytopenia was seen in 4 patients (0.8%), including 2 who developed profound thrombocytopenia. The observed time course was quite different than the acute thrombocytopenia syndrome that develops within 24 hours of abciximab administration. Second, 4 patients (0.8%) who developed profound thrombocytopenia after abciximab readministration redeveloped profound thrombocytopenia after platelet transfusion; these patients also had a prolonged (>1 week) time course before the resolution of thrombocytopenia. Both of these phenomena may also be related to the prolonged biological half-life of abciximab, an anamnestic immune response, or both; abciximab can be detected on platelets for up to 2 weeks. It thus remains critical that the practitioner obtain platelet counts in the first 24 hours after readministration, and that a high index of suspicion be maintained for the delayed development of this phenomenon. Platelet counts should be obtained when a patient presents with a syndrome consistent with thrombocytopenia within the first several weeks after abciximab readministration.

Finally, no patients developed heparin-induced thrombocytopenia. Although 3 of the 23 patients developed an increase in the titer of anti-heparin/PF4 antibodies, this incidence was less than anticipated in a population with previous exposure to heparin. By inhibiting platelet activation and PF4 release, abciximab may thus limit the formation of antigenic heparin/PF4 complexes. Abciximab may also protect against thrombosis in patients who develop heparin-dependent antibodies, but additional patients will need to be studied to confirm these findings.

The primary limitation of this evaluation was the registry design and the absence of a placebo control. A serial registry design was specifically chosen because determining the incidences of hypersensitivity and thrombocytopenia was the primary objective. The efficacy analyses, by definition, were required to be comparisons to historical reports. Also, we were not able to acquire HACA samples from all patients, although the sampling did exceed 96% (for all samples) and was without known bias. Finally, the incidence of delayed thrombocytopenia may have been underestimated; platelet counts were not systematically obtained between the day after the procedure and 4 weeks.

In summary, the therapeutic profile of abciximab with readministration in this study was similar to that observed with first-time use. However, although overall rates of thrombocytopenia were similar to those seen after first time exposure, profound thrombocytopenia (to a nadir platelet count of <20×10⁹ cells/L) occurred more frequently than with first administration. Several cases of delayed presentation or a prolonged course of recovery from thrombocytopenia were also documented. Therefore, platelet counts must not only be checked with first administration (as described in the abciximab package insert), but also with subsequent readministration. Furthermore, platelet counts may need to be checked, particularly in patients with bleeding, after the first 24 hours. Whether an alternative agent should be substituted in the retreatment indication after prior abciximab administration and whether an alternative agent would provide improved safety with at least similar efficacy have not been determined. Before recommending the substitution of alternative agents in the readministration setting, this approach will need to be investigated. Finally, on the basis of the data presented in this report, the determination of a point estimate of the incidence of hypersensitivity reactions and thrombocytopenia in HACA-positive patients with a 95% confidence interval of ±1% around zero, >3000 patients will need to be studied.
Appendix

Participating Institutions, Principal Investigators, and Study Coordinators

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References

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