Abciximab Readministration

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The IIb/IIIa receptor inhibitors have been shown to improve outcomes following percutaneous coronary intervention (PCI), particularly by decreasing periprocedural myocardial necrosis. Abciximab has been subject to multiple studies, demonstrating consistent improved early and late outcomes in multiple patient populations, including a mortality advantage in diabetics, but there has been concern about the possibility of anaphylaxis, thrombocytopenia, and reduced clinical efficacy with repeat administration of abciximab. Results of the ReoPro Readministration Registry, a prospective, phase IV, multicenter registry of 500 patients undergoing PCI who were treated with abciximab at least 7 days after a previous treatment with this same drug, support the contention that abciximab readministration is both safe and clinically efficacious and that there is no significant increase in the incidence of thrombocytopenia as compared with historical controls of trials of first abciximab administration. However, profound thrombocytopenia did occur with increased frequency as compared with historical controls, suggesting a shift from mild to profound thrombocytopenia with abciximab readministration. [Rev Cardiovasc Med. *2002;3(2):67–70*]

Key words: IIb/IIIa receptor inhibitors • Abciximab • Percutaneous coronary intervention • Thrombocytopenia

The IIb/IIIa receptor inhibitors have had a major impact on interventional cardiology. They have been studied more intensively than any other adjunctive therapy in this field and have been shown to improve outcomes following percutaneous coronary intervention (PCI), particularly by decreasing periprocedural myocardial necrosis. Abciximab was the first of this class to be approved, and it has been subject to multiple studies, demonstrating consistent improved early and late outcomes in multiple patient populations, including a mortality advantage in diabetics.[1] Abciximab is a chimeric monoclonal antibody fragment (c7E3 Fab). In the light of the chronic nature of the atherosclerotic process and the likelihood of the need for repeat procedures, there has been

concern about the possibility of anaphylaxis, thrombocytopenia, and reduced clinical efficacy with repeat administration of abciximab.[2] The following is a review of the recently published results of the ReoPro Readministration Registry.[3]

Study Methods

The ReoPro Readministration Registry was a prospective, phase IV, multicenter registry of 500 patients undergoing PCI who were treated with abciximab at least 7 days after a previous treatment with this same drug. All patients received aspirin and heparin, and PCI was performed per local standards. Platelet counts were obtained 4 hours after the abciximab bolus, the morning after the procedure, at 4 weeks, and as clinically indicated.

The diagnosis of thrombocytopenia induced by abciximab required a decrease in platelet count to less than 100 × 109 cells/L, with a fall of more than 25% from baseline and the exclusion of pseudothrombocytopenia and heparin-induced thrombocytopenia. The criteria for the diagnosis of pseudothrombocytopenia were not described in this manuscript but have been previously defined as follows: 1) a difference between the platelet count in two anticoagulants, with one having a count at least 20% lower than the count in the comparison anticoagulant; or 2) platelet clumping on a blood smear made from anticoagulated blood, but a normal platelet count on a blood smear made from nonanticoagulated blood; or 3) an unexplained drop in platelet count at 30 minutes to 4 hours after abciximab bolus, with recovery to a normal count within 4 hours after the nadir.[4] Heparin-induced thrombocytopenia was considered when cases met the criteria of Pouplard and colleagues, if heparin-dependent platelet-reactive antibodies were demonstrated using the C-serotonin release assay, or if increased levels of antiheparin/PF4 antibodies were found by enzyme-linked immunoadsorbent assay (ELISA).[5–7] The human antichimeric antibody (HACA) response of patients being retreated with abciximab was also determined at 3 to 5 days, at 4 weeks, and at 8 weeks by ELISA as previously described.[8] Clinical efficacy was defined as an angiographically successful procedure (all target lesions reduced to a final visual stenosis < 50%) without any major adverse cardiac events (death, myocardial infarction, or repeat urgent percutaneous or surgical revascularization).

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Results

No patients in this registry experienced an anaphylactic, allergic, or other hypersensitivity reaction to abciximab. Thrombocytopenia developed in 23 patients (4.6%). Approximately half of these patients (12 of 23, incidence of 2.4%) developed profound thrombocytopenia (<20,000 platelets/mm^3), and all these patients received platelet transfusions. Four patients developed thrombocytopenia after hospital discharge, with the nadir identified between days 5 and 7, including 2 patients who developed profound thrombocytopenia. Furthermore, 4 patients who developed profound thrombocytopenia were initially refractory to platelet transfusion and experienced a prolonged recovery of platelet counts. Bleeding events were reported in 13.0% of patients (65 of 500), among whom major bleeding occurred in 8 patients (1.6%). There were no reported cases of retroperitoneal or intracranial hemorrhage. Only 2 patients with a major bleeding event had thrombocytopenia, and there was no statistical correlation between major bleeding and thrombocytopenia. Clinical efficacy was achieved in 94.4% of patients, consistent with historical controls.[9–12]

The incidence of a positive HACA titer increased with abciximab readministration, and approximately one quarter of patients were HACA positive after two exposures to abciximab. But pharmacodynamic analyses (abciximab neutralization studies) showed that the abciximab dose response remained unchanged in the presence or absence of HACA, indicating that there was no clinically significant diminution of the inhibition of in vitro platelet aggregation by abciximab.

No patients in this registry experienced an anaphylactic, allergic, or other hypersensitivity reaction to abciximab.

Discussion

IIb/IIIa receptor antagonists have been extensively studied in the setting of treatment of acute ischemic syndromes and PCI.[1] They have been studied against placebo controls, conventional therapy, and in head-to-head comparisons. These studies have established several critical facts: 1) myocardial enzyme or biomarker elevation is very frequent following PCI; 2) there is a gradient of risk of subsequent morbidity and even mortality after PCI, which is

related to the degree of elevation of myocardial enzymes; 3) administration of a IIb/IIIa receptor antagonist decreases the risk of myocardial enzyme elevation; and 4) in some patient subsets, IIb/IIIa receptor antagonists improve long-term clinical outcomes.[1,13]

Therefore, it is widely accepted that the administration of these agents during PCI is valuable, but these drugs are expensive and associated with some incremental risk. Their use in all patients undergoing PCI remains controversial. Unfortunately, our ability to predict who will uniquely benefit from them remains somewhat limited. The risk of vascular complications and bleeding has been felt to be increased, particularly when heparin administration is continued, and in association with the incidence of thrombocytopenia. Rates of mild thrombocytopenia (<100,000 platelets/mm^3) in the IIb/IIIa receptor antagonist trials have averaged approximately 5%. This is comparable to the rate observed with unfractionated heparin alone. However, the rate of severe thrombocytopenia (<50,000 platelets/mm^3) varied according to the agent studied, and was approximately 2% in the abciximab trials, typically at least double that seen in the trials of eptifibatide and tirofiban.[14] The results of the Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome With Abciximab GP IIb/IIIa Blockade (EPILOG) trial suggest that the risk of severe thrombocytopenia with abciximab may be attenuated by the use of a low-dose, weight-adjusted heparin regimen, supporting the hypothesis that there is a complex interaction between abciximab and heparin. But the most worrisome clinical event following the use of abciximab is acute profound thrombocytopenia (<20,000 platelets/mm^3), typically occurring within 24 hours of drug administration. This occurs in approximately 0.7% of patients receiving abciximab, but rarely with eptifibatide or tirofiban.[14,15] The precise mechanism of this phenomenon remains unclear but is presumably immune-mediated.

The observations of this prospective multicenter registry support the contention that abciximab readministration is both safe and clinically efficacious and that there is no significant increase in the incidence of thrombocytopenia (<100,000 platelets/mm^3) as compared with historical controls of trials of first abciximab administration (composite incidence of 3.5%). However, profound thrombocytopenia (rapid decline, usually within 24 hours, to a platelet count of <20,000 platelets/mm^3) did occur with increased frequency as compared with historical controls, suggesting a shift from mild to profound thrombocytopenia with abciximab readministration. And there is some evidence to suggest that abciximab readministration may rarely be responsible for delayed and refractory profound thrombocytopenia, a finding not previously reported with the first administration of this drug.

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The authors acknowledge a number of important limitations to this study. The registry design and absence of a placebo control limit outcome analyses to comparisons

Main Points

- The ReoPro Readministration Registry was a prospective, phase IV, multicenter registry of 500 patients undergoing percutaneous coronary intervention who were treated with abciximab at least 7 days after a previous treatment with this same drug.
- No patients in this registry experienced an anaphylactic, allergic, or other hypersensitivity reaction to abciximab.
- Clinical efficacy was achieved in 94.4% of patients, consistent with historical controls.
- Abciximab dose response remained unchanged in the presence or absence of human antichimeric antibody, indicating that there was no clinically significant diminution of the inhibition of in vitro platelet aggregation by abciximab.
- The observations of this prospective multicenter registry support the contention that abciximab readministration is both safe and clinically efficacious and that there is no significant increase in the incidence of thrombocytopenia (<100,000 platelets/mm^3) as compared with historical controls of trials of first abciximab administration (composite incidence of 3.5%).
- There is some evidence to suggest that abciximab readministration may rarely be responsible for delayed and refractory profound thrombocytopenia, a finding not previously reported with the first administration of this drug.

with historical controls. It should also be noted that the incidence of delayed thrombocytopenia may have been underestimated, because platelet counts were not systematically obtained between the day after the procedure and 4 weeks. The incidence of delayed presentation in this cohort suggests that we maintain an index of suspicion for this unusual complication in patients following PCI and abciximab readministration.

Finally, it should be mentioned that this study has not clarified whether an alternative agent should be considered preferable in patients undergoing repeat PCI and glycoprotein IIb/IIIa inhibition. Three drugs are currently approved as adjunctive therapy in patients undergoing PCI, and whether one of the alternative agents might provide improved safety with similar efficacy when the need for readministration arises has not been determined. This remains an important and unanswered question. ■

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