Acute Platelet Inhibition With Abciximab Does Not Reduce In-Stent Restenosis

To the Editor:
We read with great interest the recent article by the Evaluation of ReoPro and Stenting to Eliminate Restenosis (ERASER) Investigators, in which it was reported that potent platelet inhibition with abciximab does not reduce in-stent restenosis. Abciximab is an effective anti-thrombotic agent because of its ability to bind to glycoprotein IIb/IIIa (αIIb/β3) and to inhibit platelet aggregation. Abciximab also binds to a related integrin, αvβ3, which is also known as the vitronectin receptor. The functions of this receptor include cell adhesion, proliferation, and migration and platelet-mediated thrombin generation. Thus, abciximab is expected to provide platelet-mediated effects and αvβ3-mediated effects in vivo.

Previously, we investigated changes in coagulation and platelet activation in the coronary circulation induced by stent implantation. Both aspirin and ticlopidine were administered to patients before stent implantation. Blood samples were drawn from the coronary sinus immediately before, immediately after, and 4 and 24 hours after stent implantation. Plasma levels of prothrombin fragment 1+2 (F1+2) and thrombin-antithrombin III complex (TAT), which are markers of coagulation activation, and levels of β-thromboglobulin (β-TG) and platelet factor 4 (PF4), which are markers of platelet disruption and activation, were measured. We found that F1+2 and TAT levels in blood from the coronary sinus increased significantly 24 hours after stent implantation (F1+2, from 0.73 ± 0.05 to 1.00 ± 0.10 ng/mL; TAT, from 5.01 ± 0.64 to 10.7 ± 2.26 ng/mL). However, no significant changes in β-TG and PF4 levels were observed after stent implantation (β-TG, from 60.1 ± 8.6 to 63.8 ± 9.2 ng/mL; PF4, from 27.6 ± 5.0 to 19.9 ± 6.3 ng/mL).

Gregorini et al. also reported that the combined use of aspirin and ticlopidine effectively inhibited platelet activation in patients who underwent angioplasty. In the ERASER study, all patients received aspirin before coronary intervention and ticlopidine use was left to the investigator’s discretion. Therefore, we speculate that these combined therapies sufficiently inhibit platelet activation in the coronary circulation and that any additional effects of abciximab on platelets and, thus, in-stent restenosis were not observed in the ERASER study.


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To The Editor:
Restenosis after coronary stenting may be initiated by thrombus formation followed by inflammation and smooth muscle cell infiltration. The Evaluation of ReoPro and Stenting to Eliminate Restenosis (ERASER) Investigators evaluate this hypothesis by using abciximab (ReoPro) to reduce thrombus formation after stent implantation and, thus, possibly reduce restenosis. However, 3 confounding factors must be clarified.

First, it has become standard practice to give powerful antiplatelet agents, such as ticlopidine and clopidogrel, to patients after stent insertion to reduce acute thrombosis rates. These agents act to prevent the ADP-mediated propagation of platelet activation. Platelet activation causes the release of mediators such as platelet-derived growth factor, which encourage smooth muscle proliferation (a major contributor to intimal hyperplasia). Abciximab, acting via the glycoprotein IIb/IIIa receptor, reduces platelet aggregation; it reduces activation by binding to the fibrinogen receptor. It is not necessarily true that the use of one therapy removes the need for the other. Leaving ticlopidine use to the discretion of the operator may have introduced a bias in the results, because operators might have been reluctant to use the 2 agents together. This may have had an effect on restenosis rates.

Second, infarct-related arteries have higher restenosis rates than others after percutaneous coronary transluminal angioplasty. Excluding patients with an infarct <3 days before randomisation may not have reduced this bias. Was there a difference in the number of patients randomized to each arm within 6 weeks of myocardial infarction? Were the results different for patients in this subgroup versus those who had a “cold” procedure?

Finally, the number of stents per lesion are mentioned descriptively as being equal between groups; however, the results presented are for the groups as a whole. Multiple stenting is associated with higher restenosis rates. The higher rate of multiple stents in one of the abciximab groups, although not significant, may have skewed the data against abciximab. Did a difference exist between the placebo and abciximab arms after excluding all multiple stenting procedures?

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