EDITORIAL COMMENT

The Benefits of Platelet Glycoprotein IIb/IIIa Receptor Inhibition During Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction

Drug-Specific or Class Effect?*

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For patients with ST-segment elevation (acute) myocardial infarction (STEMI), reperfusion with primary percutaneous coronary intervention (PCI) results in excellent short- and long-term outcome, predominantly because of the high rate of restoration of normal flow at the epicardial and myocardial levels (1). Despite its success, primary PCI remains fraught with obstacles because of the high thrombus burden, difficulty in initial assessment of lesion length and vessel size, and consequences of distal embolization of plaque and thrombus. Thus, adjunctive pharmacology has always been an important tool for addressing these challenges. Oral and intravenous platelet inhibitors and intravenous thrombin inhibitors have been used in various combinations to reduce thrombus size and prevent its reaccumulation after successful reperfusion.

After their introduction 2 decades ago, intravenous antagonists of the platelet glycoprotein IIb/IIIa (GPIs) (2) receptor quickly became the most researched intervention in cardiology, with numerous studies performed in a variety of clinical scenarios, ranging from adjunctive therapy to PCI in stable patients to primary PCI for STEMI (3,4). Tens of thousands of patients with varying clinical profile and acuity have been enrolled in pre- and post-marketing studies of GPIs. The prototypical agent, abciximab, is a large, chimeric antibody to the glycoprotein (GP) receptor, which sterically hinders its binding to fibrinogen in a nearly irreversible fashion, preventing platelet aggregation and potentially promoting deaggregation of recently formed platelet-rich thrombi, as occurs in STEMI (5,6). Initially, there was considerable enthusiasm about the “pleiotropic” effects of abciximab, such as inhibition of the vitronectin receptor and prevention of white blood cells aggregation to platelets and to the vascular wall (7). These interactions were hypothesized to lead to less restenosis and inflammation after PCI. Subsequent laboratory work resulted in the synthesis of smaller, cheaper molecules (peptides and non-peptides), which bind specifically and reversibly to the receptor and allow for quicker recovery of platelet function after discontinuation of infusion. As compared with abciximab’s long clearance time of 12 to 24 h, these small molecules had a clearance time of only 2 to 2.5 h, making them particularly attractive when urgent reversal of their effect was desirable. When administered in a dose sufficient to inhibit platelet aggregation by at least 80%, these compounds proved equally able as abciximab to inhibit shedding of soluble CD40 ligand, a compound associated with increased inflammation and restenosis after PCI (8).

The use of abciximab in STEMI was first studied more than 10 years ago in the RAPPORT (ReoPro and Primary PTCA Organization and Randomized) trial (9). Compared with placebo, abciximab reduced the incidence of death, reinfarction, or urgent revascularization at 7 days (11.2% vs. 5.8%, respectively, p = 0.03), but had no effect on late, nonurgent repeat revascularization. The 30-day death (2.1% vs. 2.5%) and reinfarction (4.1% vs. 3.3%) rates were similar between the groups. Earlier administration of the drug, even before angiography, seemed to result in the best outcome, in a randomized study and in a large registry. With the exception of 1 small study comparing eptifibatide with placebo (10), most of the STEMI experience has been accumulated with abciximab.

In this issue of the Journal, De Luca et al. (11) summarize the results of 6 trials comparing the outcome of primary PCI in 2,197 patients treated with abciximab, high-dose tirofiban, or eptifibatide between 2002 and 2007. In 5 studies, abciximab was compared with high-dose tirofiban (dosing regimen not approved by the Food and Drug Administration), and in 1, eptifibatide was pitted against abciximab. At 30 days death occurred in 2.2% of abciximab patients and 2.0% of tirofiban or eptifibatide patients (p = 0.66) and reinfarction occurred in 1.2% in each group (p = 0.88), without heterogeneity among the trials or evidence for publication bias. Furthermore, there was no evidence for superiority of either type of drug with respect to angiographic (restoration of Thrombolysis In Myocardial Infarction flow grade 3) or electrocardiographic (ST-segment resolution) parameters, which occurred in a high proportion.
of the patients. Major bleeding was low and comparable among the 2 groups. The authors elegantly discuss the implications of their findings and recognize that their study is significantly underpowered to detect even a 1% absolute reduction in mortality between the groups, the difference observed between lytic regimens in a landmark reperfusion study.

Currently, in the American College of Cardiology/American Heart Association guidelines abciximab use as adjunct to primary PCI carries a Class IIB (Level of Evidence: C) recommendation, while the small molecules received a Class IIB (Level of Evidence: C) recommendation (12). Are the guidelines correct? How should one interpret these results?

Using the data shown in Table 1, we can conclude that GPIs in general, and abciximab in particular (the others have not been extensively studied), are superior to placebo in improving the outcome of primary PCI. The benefit is small in absolute terms, particularly when the patients studied are relatively low-risk and cardiogenic shock is excluded. Mortality can be reduced more significantly in higher-risk patients, as shown in 1 study (13). The effect on myocardial infarction is most obvious in patients receiving percutaneous transluminal coronary angioplasty only, who are at higher risk of abrupt vessel closure soon after the procedure. Despite the putative advantages of abciximab with respect to inhibition of additional proinflammatory pathways, the small molecules appear to do as well as abciximab as far as ischemic events are concerned and the less enthusiastic attitude of abciximab in particular stems from a lack of comparative data to placebo. Finally, it is possible that on the background of aspirin and thienopyridine, the use of GPIs is likely to improve outcome, particularly when it is compared with another antithrombotic regime

The information we currently possess is sufficient to guide our practice in that GPIs are likely to improve outcome, compared with placebo or control therapy, particularly in high-risk STEMI patients, receiving the drug as early as possible after diagnosis and before primary PCI (15–17). The choice of GPI is more dependent on cost and considerations of reversibility rather than on efficacy, as long as drugs with similar ability to inhibit platelet aggregation are given. STEMI is probably the last segment of the PCI population for which GPI has a defined role, until additional studies with alternative antithrombotic regimens are performed.

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