Towards a Tailored Use of Eluted Drugs for Percutaneous Coronary Interventions

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During the past decade, glycoprotein IIb/IIIa inhibitors (GPI) have received considerable attention from clinical cardiologists and been studied in a variety of clinical settings. GP IIb/IIIa (αMβ3) serves as the receptor on platelets that binds plasma adhesive proteins, such as fibrinogen and von Willebrand factor, to permit platelet aggregation. Aggregation mediated by GP IIb/IIIa is the final common pathway of platelet activation by a variety of platelet agonists. Therefore, GPIs block platelet aggregation elicited by all stimulants, and are still currently considered the most powerful inhibitors of platelet function.1

The first of these agents, the monoclonal antibody derivative, abciximab, was originally approved for use in percutaneous coronary intervention (PCI). Subsequently, 2 other synthetic antagonists have also been approved for intravenous use: Lys-Gly-Asp (KGD)-containing cyclic heptapeptide eptifibatide, and tirofiban, developed by engineered synthesis to mimic the charge and spatial conformation of the Arg-Gly-Asp (RGD) sequence. Eptifibatide has been approved for the use in both PCI and acute coronary syndromes (ACS), whereas tirofiban is for the treatment of ACS only.2 In more recent times, however, after documentation of the efficacy of adequate thienopyridine pretreatment, the use of GPI has been mostly limited to abciximab in patients undergoing PCI for high-risk ACS.3

Abciximab is a derivative of a monoclonal antibody with molecular weight ≥47,000 Daltons and high avidity for the receptor, to which it “binds and sticks”, independent of the fall in plasma concentration.4 In addition, abciximab is not totally specific for GP IIb/IIIa, the expression of which is restricted to platelets, but it also binds to at least 2 other integrins, including αvβ3 (the so-called “vitronectin receptor”), expressed in endothelial cells and monocytes, and the leukocyte integrin αMβ2 (MAC-1), one of the main ligands for intercellular adhesion molecule-1 (ICAM-1),4 thereby inhibiting inflammatory responses and smooth muscle cell proliferation after vascular injury. This may confer abciximab peculiar pharmacological properties, not shared by eptifibatide and tirofiban.5

The possibility that abciximab reduces neointimal hyperplasia seemed to translate into clinical benefit after documentation of a significant reduction of restenosis in patients who were receiving the drug and were enrolled in the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) study.6 However, further studies in the stent era failed to confirm this finding.7

More recently, in search of ways to reduce the neointimal formation leading to restenosis, stents have been used as vehicles for local drug delivery. Drug-eluting stents (DES) are coated stents capable of releasing antiproliferative agents into the surrounding tissues. Several clinical trials have documented a 3- to 4-fold reduction in the rate of in-stent restenosis after PCI with DES compared with bare-metal stenting (BMS).8 However, the drugs eluting from the stent inhibit strut endothelialization, making the vascular surface potentially thrombogenic for long periods of time.9 This documented delayed endothelialization of the stent struts has raised considerable concern that DES may be susceptible to late thrombosis. The occurrence of late DES occlusion during post-marketing surveillance, and the extreme severity of the ensuing clinical consequences, prompted the American Food and Drug Administration to release a public warning on this issue.10 Adjunctive antiplatelet therapy with aspirin and a thienopyridine limits the occurrence of late DES thrombosis to 0.3–0.5%/year, which is comparable to BMS. Nevertheless, prolonged dual antiplatelet therapy increases the patient’s bleeding risk. Therefore, a stent coated with a drug that has both antithrombotic and antiproliferative properties would still be extremely attractive at the present time.

In a porcine model of coronary artery restenosis, Hong et al11 compared an abciximab-coated stent with both sirolimus- and paclitaxel-eluting stents. Histopathologic analysis was performed at 28 days, and showed that the abciximab-coated stent had inhibited inflammatory cell infiltration and neointimal hyperplasia similar to other DES; the neointimal area normalized to injury, as well as inflammation scores and the score of inflammatory cell counts normalized to injury, was similar among the 3 stent groups. Unfortunately, this preclinical study is still the only comparison available between abciximab-coated stent and DES, as other clinical studies have always only compared abciximab-coated stents with BMS.

The best scenario in which a platform eluting a drug with both antiinflammatory and antithrombotic capabilities should be tested is acute myocardial infarction (AMI). Abciximab-coated stents were compared with BMS in a small population of patients (n=96) receiving angioplasty during AMI. The clinical results of the stent coated with abciximab (ReoPro®) in AMI was accompanied by reduced target lesion revascu-

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larization, percent diameter stenosis, late loss and neointimal hyperplasia at follow-up. No stent thrombosis was reported. In a mechanistic study, Hong et al. documented that restenosis (assessed by angiography) and in-stent neointimal hyperplasia (assessed by intravascular ultrasound) were 14% and 2±1.6 mm², respectively, after the use of abciximab-coated stents, almost half when compared with BMS (28.6% and 3.4±1.7 mm², respectively). In the present issue of the Journal, Kim et al. report the 2-year follow-up of the first population of patients treated earlier with PCI and abciximab-coated stent for various indications. Subjects were randomized to abciximab-coated or BMS. The 2-year results confirm the safety of the abciximab-coated stent; despite the use of dual antiplatelet therapy (aspirin and a thienopyridine) for a short time (only 2 months) in both groups, no stent thrombosis was observed and major adverse cardiac events (death, MI or coronary revascularization) had a trend toward a reduction in the abciximab-coated stent group compared with BMS.

Unfortunately, the present study shares the limitations of the entire literature on abciximab-coated stents: despite having been available for more than 10 years, these devices have been tested until now only in a very limited patient population, in trials always comparing these devices with BMS, and only by the same group of investigators.

Why is this device not sufficiently attractive to the market of interventional cardiology to be produced and then tested in larger-scale trials? We hope that the answer is not in the insidious search for DES producing “absent” neointimal hyperplasia, a concept that has already suffered the high cost of excess late thrombosis. Perhaps, as highlighted by Thomas H. Lee in his Perspective on the “me-too products”, the paradox is that market late-comers are usually better accepted when they differ trivially from earlier products, with the hope of strong competition among different products and a final overall reduction of costs for the health system. Unfortunately, we have never actually seen such real price wars ultimately driving healthcare costs much lower.

Apart from the cost issue, the scientific community should resist the temptation to crown one single “best” device for all-comers, but try to choose, from the available armamentarium, which device is best suited for each patient in each clinical scenario. In this view, the abciximab-coated stent would represent an interesting option, as it shows prolonged antithrombotic properties at the price of a moderate vascular hyperplastic response. Unfortunately, without the interest of some industry that would invest in a true clinical comparative validation of this concept, these potentials will remain unfulfilled.

References