Unsticking platelets: the role of glycoprotein IIb/IIIa receptor blockade

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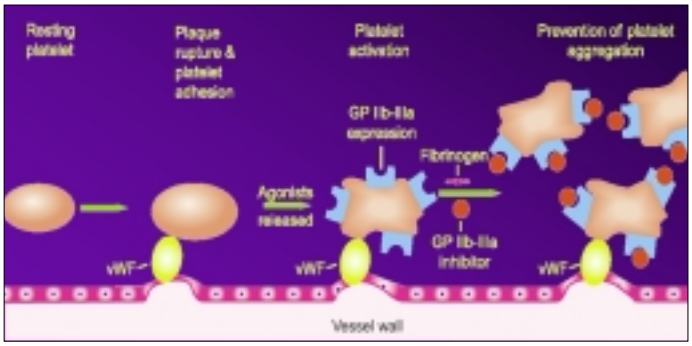
Technology: Glycoprotein IIb/IIIa receptor antagonists of platelets

Use: The activation of platelet glycoprotein IIb/IIIa receptors results in rapid thrombosis through specific binding of its ligand, fibrinogen. The use of the Fab fragment of the mouse/human chimeric monoclonal antibody 7E3, now known as the pharmaceutical abciximab (ReoPro), and several small-molecule synthetic IIb/IIIa inhibitors blocks platelet receptors and thereby attenuates prothrombotic states. This procedure was developed by Barry Coller, who demonstrated that abciximab prevented platelet aggregation by inhibiting fibrinogen binding.[1] Currently, these agents are administered intravenously to patients with acute coronary syndromes for periods of several hours to 2–3 days.



Transition from resting state through adherence to the vessel wall with subsequent activation of the IIb/IIIa receptor on the platelet surface in concert with a change in platelet morphology. The subsequent occupancy of the IIb/IIIa receptor by a receptor blocker interferes with the fibrinogen ligand, which would ordinarily facilitate the linkage of receptors and thereby produce aggregation. vWF = von Willebrand factor. (Reprinted from White[8] with permission.)

History: This novel approach to managing acute coronary syndromes was stimulated by several factors. There was an increasing appreciation of both the role of platelet aggregation in thrombosis and the relative resistance of platelet-rich thrombi to conventional therapy with fibrinolytics.[2] In addition, the pathogenesis of Glanzmann's thrombasthenia became better understood, and it was realized that these patients who had profound defects in platelet aggregation, yet maintained platelet adhesion, had platelet membrane glycoprotein deficiencies; these deficiencies were further localized to the platelet surface receptors. Finally, despite the efficacy of aspirin and other platelet antagonists, major vascular complications often ensue in patients receiving these therapies, perhaps emphasizing that they are only partial inhibitors that offer suboptimal protection from platelet-mediated thrombosis. Accordingly, a strategy that would inhibit the final common pathway of platelet aggregation through glycoprotein IIb/IIIa blockade carried great promise.

With his newly developed receptor-blockade assay Coller discovered that blocking approximately 80% of the platelet receptors (there are at least 40 000 receptors on the surface of each platelet) led to the virtual elimination of platelet aggregation, but only minimally prolonged bleeding time. In vitro studies and arterial thrombotic models followed; the model of cyclic flow in the coronary artery of the dog developed by James Folts and a model of reocclusion following fibrinolytic therapy in a canine acute myocardial infarction simulation demonstrated dramatic therapeutic benefits. Clinical applications soon followed. In a systematic overview of 16 clinical trials to assess the effects of these compounds in patients with ischemic heart disease, Kong and colleagues[3] reported a 35% reduction in risk of 30-day death and myocardial infarction. This benefit proved to be durable and has been reproduced in various patient groups undergoing coronary interventions, as well as in patients with unstable angina and non-ST elevation myocardial infarction. Abciximab (ReoPro) is now in general use for percutaneous coronary interventions in Canada, and the small-molecule synthetic agents eptifibatide (Integrilin) and tirofiban (Aggrestat) are available for the management of unstable angina in the United States. Both have recently been approved for use in Canada.[4,5]

Problems: Because these agents are expensive, the identification of patients at greatest risk and most likely to benefit is desirable; these include patients with elevated cardiac markers such as troponin T or I, high-risk ST-segment changes and recurrent or refractory symptoms. Thrombocytopenia is a recognized, infrequent and usually reversible complication associated with the use of these inhibitors.[6]

Prospects: Future prospects involve the use of these agents in conjunction with fibrinolytic therapy for acute ST-elevation myocardial infarction. Phase II studies demonstrate enhanced coronary angiographic patency with lower doses of fibrinolytics; hence, the prospect of reducing the risk of intracranial hemorrhage and facilitating safer coronary intervention[4] with

such a treatment strategy is most appealing.[7] This is now being tested in a large phase III international trial (GUSTO [Global Strategies to Open Occluded Coronary Arteries] IV) in which a number of Canadian centres are participating.

The use of platelet glycoprotein IIb/IIIa inhibitors is a major therapeutic advance in the management of arterial thrombosis. Several issues remain to be addressed, however. Is this a class effect or does the antibody have specific characteristics? What is the optimal duration and dose of therapy? How should therapy best be monitored? Can the acute benefits be extended by conversion to pharmacologically active oral agents that are administered long-term?

Competing interests: Dr. Armstrong received research grants for coordinating the PURSUIT and GUSTO IV research trials in Canada and received speaker fees and educational grants from Schering Plough.

References

1. Coller BS. Blockade of platelet GPIIb/IIIa receptors as an antithrombotic strategy. *Circulation* 1995;92:2373-80.
2. Lefkovits J, Plow EF, Topol EJ. Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine [review]. *N Engl J Med* 1995;332(23):1553-9.
3. Kong DF, Califf RM, Miller DP, Moliterno DJ, White HD, Harrington RA, et al. Clinical outcomes of therapeutics agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. *Circulation* 1998;98:2829-35.
4. PURSUIT trial investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998; 339(7):436-43.
5. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998;338(21):1488-97.
6. Madan M, Berkowitz SD, Tcheng HE. Glycoprotein IIb/IIIa Intregrin blockade. *Circulation* 1998;98:2629-35.
7. Antman EM, Giugliano RP, Gibson CM, McCabe CH, Coussement P, Kleiman NS, et al. Abciximab facilitates the rate and extent of thrombolysis: results of the thrombolysis in myocardial infarction (TIMI) 14 trial. The TIMI 14 Investigators. *Circulation* 1999;99(21):2720-32.
8. White HD. Unmet therapeutic needs in the management of acute ischemia. *Am J Cardiol* 1997;80(4A):2B-10B.

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