Current Perspective

Synthetic Inhibitors of Platelet Glycoprotein IIb/IIIa in Clinical Development

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Abstract—Activation of the platelet glycoprotein (GP IIb/IIIa) receptor on the platelet surface is the final pathway of platelet aggregation, regardless of the initiating stimulus. Inhibitors of GP IIb/IIIa receptors include monoclonal antibodies (abciximab) against this receptor and peptidic and nonpeptidic synthetic specific receptor blockers. Abciximab exchanges between and binds to platelets for as long as 2 weeks, whereas synthetic GP IIb/IIIa inhibitors inhibit ex vivo platelet aggregation for only a few hours after the end of infusion, but some have the advantage of also being orally active. In the secondary prevention of atherothrombosis, large-scale trials were successfully conducted with aspirin, dipyridamole, ticlopidine, and clopidogrel. In the first large-scale trials with GP IIb/IIIa inhibitors, abciximab was investigated. In aggregate, synthetic GP IIb/IIIa inhibitors, combined with aspirin and heparin, were shown to reduce ischemic events in patients with high- and low-risk coronary intervention, stents, unstable angina, and non–Q-wave infarction. With short-term use of synthetic GP IIb/IIIa inhibitors, there is no suppression of clinical evident restenosis 6 months after the end of treatment. With the doses currently used, bleeding occurs more often with the synthetic GP IIb/IIIa inhibitors (used for 3 days) than with abciximab (used for 12 hours), but there are no direct comparisons between these drugs. (Circulation. 2000;102:e76-e80.)

Key Words: platelet glycoprotein IIb/IIIa ■ fibrinogen ■ platelet aggregation inhibitors ■ von Willebrand factor

Unstimulated platelets have 50,000 to 80,000 glycoprotein (GP) IIb/IIIa receptors on their surface. Exposure of these receptors is the final common end point of all pathways leading to platelet aggregation (the Figure). All ligands for the GP IIb/IIIa receptor, such as fibrinogen, von Willebrand factor, endothelium-derived factors, vitronectin, and thrombospondin, bind through their arginine-glycine-aspartic acid (RGD) recognition site; a larger recognition sequence (lysine-glycine-alanine-glycine-aspartic acid-valine, or KQAGDV) is specific for the gamma chain of fibrinogen. Except for some tumor cells, the GP IIb/IIIa receptor is confined to cells of the megakaryocyte/platelet lineage.

Lamifiban

Lamifiban (Ro 44–9883, Hoffmann-La Roche) is a synthetic nonpeptidic compound of low molecular weight (0.468 kDa) with a Kd of 9.4 nmol/L. In a Canadian study, lamifiban (1, 2, 4, and 5 μg/min IV) protected 365 patients with unstable angina from severe ischemic events during a 2- to 5-day infusion (all doses combined 3.3% versus 8.1%, P=0.04) and reduced the incidence of death and myocardial infarction at 1 month (3.7% versus 8.1%). No clear dose-related incremental clinical benefit could be documented in this small study, but more major bleeding (2.9% versus 0.8%) and significantly more minor bleeding (11.1% versus 1.6%, P=0.002) were noted in the high-dose lamifiban groups. The lack of a dose-related correlation to clinical benefit and higher bleeding incidence in the highest-dose lamifiban patients were confirmed in the Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON-A) trial. In total, 2282 unstable angina and non–Q-wave myocardial infarction patients were randomly assigned to lamifiban in a 2×2 factorial design—low-dose (1 μg/min) with and without heparin versus high-dose (5 μg/min) with and without heparin—or to placebo and heparin. All patients received aspirin. The relative benefit for reduced death or myocardial infarction at 30 days was lowest for those assigned to low-dose lamifiban plus heparin (relative reduction, 12%) compared with control subjects. At 6 months, this composite end point was again lowest in the low-dose lamifiban plus heparin group (P=0.025; relative reduction, 30%) and intermediate for those assigned to high-dose lamifiban with or without heparin (P=0.45) compared with control subjects. The combination of high-dose lamifiban and heparin resulted in more major or intermediate bleeding (12.1% versus 5.5%, P=0.002) and, at 6 months, in a similar rate of death or myocardial infarction (18%) compared with control subjects (18%). Conversely, low-dose lamifiban and heparin yielded similar bleeding rates as in the control group but had fewer ischemic events (12.6% versus 17.9%) at 6 months. Heparin did not contribute to lamifiban efficacy but did cause more bleeding; durability and incremental rate benefit have also been observed in the Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications (EPIC) trials evaluating monoclonal antibodies against GP IIb/IIIa in angioplasty patients.

The Platelet Aggregate Receptor Antagonist Dose Investigation for Reperfusion Gain in Myocardial Infarction (PARADIGM)
angioplasty. The primary composite end point at 30 days was nonfatal myocardial infarction and the need for repeated revascularization (7.1% versus 17.1%, \( P = 0.034 \)). However, mortality was significantly reduced in patients receiving tirofiban (2.3% versus 3.6%, \( P = 0.02 \)). Major bleeding occurred in 0.4% of the patients in both groups, and reversible thrombocytopenia was found in 11.1% and 0.4% (\( P = 0.04 \)) of the tirofiban and control groups, respectively. In the Platelet Receptor Inhibition for Ischemic Syndrome Management Plus (PRISM-PLUS) trial, 1915 patients with acute coronary syndromes, all on aspirin, were randomized to tirofiban plus heparin or either drug. Study drugs were given for a minimum of 48 hours before and 48 to 96 hours after PTCA. The study arm of tirofiban without heparin was stopped prematurely because of excess mortality at 7 days. There was a significant reduction in death, myocardial infarction, and refractory cardiac ischemia in the patients treated with tirofiban plus heparin at 7 days, 30 days, and 6 months. The angiographic substudy in PRISM-PLUS also indicated that tirofiban-treated patients had significantly fewer angiography-detected intracoronary thrombi 65±17 hours after randomization and improved blood flow in the culprit coronary artery.

**Tirofiban**

Tirofiban (MK-383, L-700,462 Aggrastat, Merck and Co) is a tyrosine derivative (MW 95) that inhibits fibrinogen binding to GP IIb/IIIa (\( K_d \) 0.15 nmol/L). The plasma half-life is \( \sim 90 \) minutes.

The dosage regimen of tirofiban was studied in patients with PTCA. They were randomized to receive placebo or tirofiban 5-\( \mu \)g/kg bolus IV, then 0.05 \( \mu \)g/kg bolus IV of 0.1-\( \mu \)g/kg bolus, then 0.1 \( \mu \)g/kg bolus IV, or 10-\( \mu \)g/kg bolus, and then 0.15 \( \mu \)g/kg bolus IV for 36 hours. All 93 patients also received oral aspirin (325 mg) before angioplasty and intravenous heparin. Platelet aggregation was inhibited by 72% to 96% 5 minutes after tirofiban administration was begun. There were too few adverse ischemic events in the study to evaluate efficacy. Bleeding events occurred in 4.8%, 3.3%, and 13.6% of patients receiving the lowest, middle, and highest doses of tirofiban, respectively, compared with 5% of placebo recipients.

The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial was a randomized, double-blind, placebo-controlled trial of tirofiban in patients undergoing coronary interventions within 72 hours of presentation with unstable angina pectoris or acute myocardial infarction. All patients received aspirin and intravenous heparin and were randomized to tirofiban (bolus of 10 \( \mu \)g/kg followed by a 36-hour infusion of 0.15 \( \mu \)g/kg · min⁻¹) or placebo. Two days after angioplasty, the tirofiban group had a 38% relative reduction in the composite end point (death, myocardial infection, need for revascularization) (\( P = 0.05 \)), and at 7 days, there was a 27% relative reduction (\( P = 0.02 \)), largely because of a reduction in nonfatal myocardial infarction and the need for repeated angioplasty. The primary composite end point at 30 days was reduced by 16% (\( P = 0.16 \)). The bleeding observed with tirofiban was not statistically different from that observed with placebo.

In the Platelet Receptor Inhibition for Ischemic Syndrome Management (PRISM) study, 3232 patients with unstable angina and non-Q-wave myocardial infarction were treated before PTCA with a 48-hour infusion of tirofiban or heparin. All patients received aspirin. The composite end point of refractory unstable angina, myocardial infarction, or death was 32% lower at 48 hours (\( P = 0.01 \)). At 30 days, the frequency of the composite end point was similar in the 2 groups (15.9% versus 17.1%, \( P = 0.34 \)). However, mortality was significantly reduced in patients receiving tirofiban (2.3% versus 3.6%, \( P = 0.02 \)). Major bleeding occurred in 0.4% of the patients in both groups, and reversible thrombocytopenia was found in 11.1% and 0.4% (\( P = 0.04 \)) of the tirofiban and control groups, respectively. In the Platelet Receptor Inhibition for Ischemic Syndrome Management Plus (PRISM-PLUS) trial, 1915 patients with acute coronary syndromes, all on aspirin, were randomized to tirofiban plus heparin or either drug. Study drugs were given for a minimum of 48 hours before and 48 to 96 hours after PTCA. The study arm of tirofiban without heparin was stopped prematurely because of excess mortality at 7 days. There was a significant reduction in death, myocardial infarction, and refractory cardiac ischemia in the patients treated with tirofiban plus heparin at 7 days, 30 days, and 6 months. The angiographic substudy in PRISM-PLUS also indicated that tirofiban-treated patients had significantly fewer angiography-detected intracoronary thrombi 65±17 hours after randomization and improved blood flow in the culprit coronary artery.

**Eptifibatide**

Eptifibatide (Integrilin, Cor Therapeutics, Key Pharmaceuticals) is a disulfide-linked heptapeptide (MW 800) whose cyclic structure increases the affinity to GP IIb/IIIa receptors (\( K_d \) 100 mmol/L). A higher dissociation constant for Integrilin compared with abciximab results in an almost linear relationship between the plasma and the platelet-bound drug pool.

Eptifibatide affords rapid, competitive, and reversible platelet inhibition when administered with concomitant aspirin and heparin in patients undergoing elective percutaneous coronary intervention. Fifty-four such patients were randomized in a pilot trial to receive placebo or a bolus of eptifibatide (90 to 180 \( \mu \)g/kg IV) plus an 18- to 24-hour infusion of 0.5 to 1 \( \mu \)g · kg⁻¹ · min⁻¹. The procedure was successful in 94% and 96% of patients, respectively. The Integrilin to Manage Platelet Aggregation to Combat Thrombosis (IMPACT-I) study in 150 patients undergoing elective coronary intervention supported the potential efficacy of eptifibatide (12.2% in the placebo group versus 4.1% end-point events, \( P = 0.13 \)) administered as a 90-\( \mu \)g/kg bolus followed by 1.0 \( \mu \)g · kg⁻¹ · min⁻¹ for 12 hours. This study, however, was associated with an incidence of any bleeding twice that of placebo-treated patients. Moreover, 3 patients developed thrombocytopenia. IMPACT-II was a large trial in 4010 low- and high-risk patients undergoing an intervention procedure under cover of aspirin and heparin. The purpose was to compare the additional effect of 2 infusion regimens of eptifibatide (135-\( \mu \)g/kg bolus followed by an infusion of 0.5 or 0.75 \( \mu \)g · kg⁻¹ · min⁻¹ for 20 to 24 hours) and placebo on mortality, myocardial infarction, and need for urgent revascularization.
ization 30 days after drug administration. Results show a significant effect of both drug regimens at 24 hours and a statistically significant effect of the low-dose (19% reduction, \( P=0.035 \)) but not the high-dose (13% reduction) regimen at 30 days. Treatment with eptifibatide did not result in any increase in major bleeding compared with placebo notwithstanding aspirin and heparin administration in all patients and an infusion of eptifibatide twice as long as in IMPACT-I.

A randomized trial compared aspirin and low-dose (45-μg/kg bolus and 0.5 μg·kg\(^{-1}\)·min\(^{-1}\)) and high-dose (90-μg/kg bolus and 1.0 μg·kg\(^{-1}\)·min\(^{-1}\)) eptifibatide for 24 to 72 hours for treatment of unstable angina.\(^{14} \) All 227 patients completing the research protocol received standard medical therapy for unstable angina, including intravenous heparin, in addition to the test drug but aspirin only after termination of the study drug. The number and duration of ischemic events were measured over the first 24 hours of treatment by Holter monitoring. Patients on high-dose eptifibatide had a mean (±SD) of 0.24±0.11 ischemic events per 24 hours, whereas patients on aspirin had 1.0±3.3 events (\( P<0.05 \)) and patients on low-dose eptifibatide had 0.83±0.32 events. The high-dose eptifibatide group also had shorter ischemic episodes than the aspirin-treated group (8.4±5.3 versus 26.23±9.8 minutes, \( P=0.01 \)). Bleeding complications were few, mostly ecchymoses at sites of intravenous lines.

The large Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrin Inhibition in Acute Myocardial Infarction (PURSUIT) trial was conducted to evaluate the efficacy of eptifibatide in preventing death or myocardial infarction at 30 days in \( \approx 11000 \) patients hospitalized with unstable angina or non-Q-wave myocardial infarction.\(^{15} \) The doses were twice those used in IMPACT-II, because the goal was to achieve 80% platelet inhibition. In PURSUIT, patients were randomized to 1 of 3 groups: placebo, low-dose eptifibatide (180-μg/kg bolus and 1.3-μg·kg\(^{-1}\)·min\(^{-1}\) infusion), or high-dose eptifibatide (180-μg/kg bolus and 2-μg·kg\(^{-1}\)·min\(^{-1}\)) for \( \leq 72 \) hours or \( \leq 96 \) hours if percutaneous coronary intervention (stent and/or PTCA) was performed. At a prespecified review after 3218 patients were recruited, the low-dose arm was stopped given the safety of the high-dose arm. The primary composite end point of death or reinfarction at 30 days was reached in 15.7% of the 4739 patients in the placebo group and in 14.2% of patients in the eptifibatide group (\( P=0.042 \)). Eptifibatide was associated with a moderate increase in major and minor bleeding. The early benefit is maintained without attenuation through 6 months. Eptifibatide was also shown in a small study of 180 patients with acute myocardial infarction to enhance the incidence (TIMI grade 3 flow at 90 minutes: 66% versus 39%, \( P=0.006 \)) and speed of reperfusion when combined with accelerated alteplase, aspirin, and intravenous heparin without excess bleeding (IMPACT-TAMI).\(^{16} \)

**Xemilofiban**

Xemilofiban (SC-5468A, Searle Co) is an ethyl-ester prodrug with an RGD-containing peptide sequence that is recognized by the platelet GP IIb/IIIa receptor. The active molecule SC-57101B has a terminal elimination half-life of 16 to 18 hours. Patients with stabilized ischemic syndromes, all on aspirin, were given 30 to 50 mg xemilofiban BID orally in the Safety of Xemilofiban in Acute Coronary Research (SOAR) trial. They were randomized to study drug treatment within 120 hours after the index event (unstable angina and Q-wave and non-Q-wave myocardial infarction). A good dose response in terms of ex vivo ADP-induced platelet aggregation was obtained.\(^{21} \) With the highest dose, 2 of 45 patients (4%) stopped the study drug because of bleeding.

The primary objective of the Xemilofiban in Patients With Unstable Coronary Syndrome (OPUS) trial (TIMI 16) was to test the hypothesis that oral xemilofiban (2 dosing strategies) plus aspirin will prevent at 30 days major cardiovascular events (death, subsequent myocardial infarction, recurrent ischemia requiring rehospitalization, urgent revascularization, or stroke) compared with placebo plus aspirin during long-term treatment in 12 000 patients with unstable coronary syndromes. One year after the start of the trial, 10 302 patients were randomized and further recruitment was stopped because no significant difference in the composite end point was obtained between the 3 trial groups (to 300 days: 20.6% and 20.5% in patients treated with xemilofiban, 21.2% in placebo group). Further development of xemilofiban was halted because the death rate in the 2 xemilofiban groups was almost significantly higher than in the placebo group.

**Sibrafiban**

Sibrafiban (Ro 48–3657, Hoffmann-La Roche, G7333 Genentech) is an orally active, nonpeptidic, double prodrug that is converted in 2 enzymatic steps in the active compound Ro 44–3888.\(^{22} \) In the TIMI 12 trial, several oral dosing regimens were tested for 28 days before and to 25 mg TID for 30 days after angioplasty. All patients also received aspirin and heparin. More profound inhibition of platelet aggregation for a period of \( \leq 3 \) days was obtained compared with aspirin alone. At all doses tested, acute major bleeding was encountered.\(^{19} \)

After PTCA, 605 patients were enrolled in the Oral Glycoprotein IIb/IIIa Receptor Blockade to Inhibit Thrombosis (ORBIT) study, all on aspirin, and randomized to placebo or 15 or 20 mg xemilofiban (first 2 weeks, 3 times daily; after 2 weeks, twice daily) for 2 weeks. At 3 months, cardiac events occurred in 11% of the placebo group and 8% in the low-dose and 5% in the high-dose xemilofiban group (\( P=0.006 \)).\(^{20} \)

The Evaluation of Oral Xemilofiban in Controlling Thrombotic Events (EXCITE) trial was a blinded, placebo-controlled trial that was to enroll 7200 patients at 450 sites in 17 countries. The combined event rate of death and myocardial infarction at 6 months was 9.1% for placebo, 9.2% for xemilofiban (10 mg), and 8.2% for xemilofiban (20 mg). The effectiveness of oral xemilofiban plus aspirin was compared with aspirin alone in reducing complications during PTCA and in preventing recurrent events for \( \leq 6 \) months. This trial did not indicate the effectiveness of xemilofiban, and development of the compound has been abandoned.

**Orbofiban**

Orbofiban (SC-57099B, Searle Co) is an ethyl-ester prodrug with an RGD-containing peptide sequence that is recognized by the platelet GP IIb/IIIa receptor. The active molecule SC-56632B has a terminal elimination half-life of 16 to 18 hours. Patients with stabilized ischemic syndromes, all on aspirin, were given 30 to 50 mg orbofiban BID orally in the Safety of Orbofiban in Acute Coronary Research (SOAR) trial. They were randomized to study drug treatment within 120 hours after the index event (unstable angina and Q-wave and non-Q-wave myocardial infarction). A good dose response in terms of ex vivo ADP-induced platelet aggregation was obtained.\(^{21} \) With the highest dose, 2 of 45 patients (4%) stopped the study drug because of bleeding.

The primary objective of the Orbofiban in Patients With Unstable Coronary Syndrome (OPUS) trial (TIMI 16) was to test the hypothesis that oral orbofiban (2 dosing strategies) plus aspirin will prevent at 30 days major cardiovascular events (death, subsequent myocardial infarction, recurrent ischemia requiring rehospitalization, urgent revascularization, or stroke) compared with placebo plus aspirin during long-term treatment in 12 000 patients with unstable coronary syndromes. One year after the start of the trial, 10 302 patients were randomized and further recruitment was stopped because no significant difference in the composite end point was obtained between the 3 trial groups (to 300 days: 20.6% and 20.5% in patients treated with orbofiban, 21.2% in placebo group). Further development of orbofiban was halted because the death rate in the 2 orbofiban groups was almost significantly higher than in the placebo group.
in patients with acute coronary syndromes. A clear dose-response relationship was seen with higher drug levels, correlating with higher levels of platelet inhibition and higher levels of bleeding complications.22 The peak blood level was achieved ~6 hours after ingestion. With the twice-daily dosing, the degree of inhibition was sustained, with 70% inhibition of ADP-induced platelet aggregation at 24 hours. Similar to inhibition of platelet aggregation, a dose response was demonstrated for prolongation of the bleeding time. A clinically significant major or minor bleeding rate occurred at the doses that achieved 70% to 80% platelet inhibition (5 to 10 mg BID). Sibrafiban Versus Aspirin to Yield Maximum Protection From Ischemic Heart Events post Acute Coronary Symptoms (SYMPHONY-1) is a double-blind, aspirin-controlled study enrolling 9000 patients at sites in 40 countries. The effectiveness of oral sibrafiban (body weight– and renal function–adjusted dosages) vs aspirin in achieving secondary prevention at 3, 6, and 12 months is the primary end point. A SYMPHONY-2 trial had been started but was stopped because SYMPHONY-1 did not demonstrate superiority over aspirin after 3 months of blinded therapy.

**Fradafiban**

Fradafiban (BIBU-52 ZW, Boehringer Ingelheim) has only very limited oral activity, probably because of its high polarity and thus poor absorption after oral ingestion. Esterification of the carboxyl group and acylation of the amino group of fradafiban led to the far-less-polar prodrug lefradafiban (BIBU-104-XX), which has to be converted metabolically to fradafiban for platelet inhibition. Esterases, but not cytochrome P450–dependent enzymes, are involved in the conversion of lefradafiban to fradafiban in vivo.23

The activity and plasma levels of fradafiban and lefradafiban were evaluated in 130 healthy male subjects. Fradafiban 1 to 15 mg continuously infused over 30 minutes reversibly inhibited platelet aggregation in platelet-rich plasma ex vivo in response to ADP and collagen.24 Single oral doses of lefradafiban inhibited ADP-induced aggregation after 50 mg by 59%, after 100 mg by 90%, and after 150 mg by 99% 8 hours after administration. Correlations between activity and fradafiban plasma levels were identical after fradafiban and lefradafiban treatment. After day 1, oral lefradafiban treatment for 7 days inhibited aggregation by 31% (25 mg TID), 53% (50 mg TID), and 88% (75 mg TID) just before the next dose. A similar correlation between activity and fradafiban plasma levels was observed at days 1, 2, and 7. Thus, oral administration of lefradafiban maintains the potent platelet GP IIb/IIIa antagonism of fradafiban during treatment of healthy subjects for 1 week without signs of loss of the antiplatelet activity. FROST-1, FROST-2, and ICE are ongoing clinical trials with fradafiban.

**L-738,167**

L-738,167 (Merck Research Laboratories) is a highly potent and intrinsically active nonpeptidic antagonist of GP IIb/IIIa.25 The terminal plasma half-life after intravenous administration to dogs was estimated to be ~4 days. The prolonged retention of L-738,167 in blood despite a relatively short release time from the receptor has been proposed to result from the rapid recapture of L-738,167 by the high concentration of platelet GP IIb/IIIa receptors before it is cleared from the plasma.26

The lower, 30-μg/kg oral L-738,167 dose, which significantly reduced the incidence of occlusive thrombosis and/or reduced thrombus mass in a canine coronary artery thrombosis model, was associated with a sustained but modest 2- to 3-fold increase in template bleeding time.27

**Roxifiban**

DMP-754 (Du Pont Merck Pharmaceutical Co) is an isoxazolylacetamide and an ester prodrug that, on conversion to its active form XV459 (roxifiban), appears to be a competitive, high-affinity (Kᵦ = 1 to 2 nmol/L), and selective inhibitor of GP IIb/IIIa.28 When administered to dogs at 1.0 mg/kg IV, both DMP 754 and roxifiban significantly (P<0.001) extended bleeding time to >30 minutes compared with a basal bleeding time of 3 to 4 minutes. Template bleeding time increased to 6 to 8 minutes after administration of 0.1 mg/kg PO of DMP 754, extended to 12 to 15 minutes after 0.4 mg/kg PO of roxifiban, and extended to 15 to 20 minutes after 0.3 mg/kg PO of DMP 754. The effect on the bleeding time is reversible while maximal inhibition of platelet aggregation is maintained.29

Roxifiban demonstrated significant antithrombotic efficacy (P<0.001) when administered intravenously or orally at relatively low doses in different settings or arterial thrombosis in canine.30 After bolus administration of roxifiban in dogs, plasma concentration declined polynomials with a terminal half-life of 12 hours. Clinical trials with roxifiban (ROCKET-1, ROCKET-2, GAP) are being conducted.

**Lotrafiban**

SB-214857 (SmithKline Beecham) is a nonpeptidic selective antagonist of the human platelet fibrinogen receptor GP IIb/IIIa. The binding is saturable, has high affinity (Kᵦ =2.5 nmol/L), and is reversible. The affinity of SB-218857 is >1000-fold greater for GP IIb/IIIa integrin than for other adhesive integrins such as αvβ3 and αvβ5.

In a dose-finding study (Antiplatelet Useful Dose Study [APLAUD]), atherosclerotic patients, all on aspirin, were randomized to 5, 20, 50, or 100 mg SB-214857 or oral placebo twice daily for 12 weeks. Platelet aggregation was dose dependently inhibited, 87% after 50 mg and 100% after 100 mg. Major bleeding was noted in 12% of patients on 100-mg oral dose and in 2.9% after 50-mg oral dose versus 2.1% in placebo-treated patients. Thrombocytopenia occurred in 0.6% of the 349 patients exposed for 12 weeks to lotrafiban.

The large-scale, placebo-controlled, double-blind, 2-arm trial Blockade of the Receptor to Avoid Vascular Occlusion (BRAVO) in atherosclerotic patients is halfway. Two doses of lotrafiban are tested. Patients will begin therapy on either 30 or 50 mg lotrafiban versus placebo BID, depending on age and/or renal function. All patients will receive concomitant aspirin and will be followed up for 6 months to 2 years (3500 subjects per treatment group).

**GP IIb/IIIa Receptor Blockers in Perspective**

At least a dozen GP IIb/IIIa inhibitors have been synthesized. Cyclic compounds are ~10 times more potent and more stable than linear analogues, although not orally active. They also exhibit a higher selectivity for GP IIb/IIIa receptors compared with the vitronectin receptor.

Intravenous GP IIb/IIIa inhibitors are desirable when rapid and reliable platelet inhibition is requested, but oral inhibitors lend themselves to long-term administration and secondary
prevention after interventional procedures. Thus, orally active synthetic GP IIb/IIIa inhibitors vastly expand the potential area of application of this class of platelet inhibitors. It remains to be seen, however, whether long-term inhibition of GP IIb/IIIa receptors rendering patients similar to those with congenital Glanzmann thrombasthenia disorder would be associated with the bleeding problems encountered by the latter group.

The remarkable long-term benefit obtained with abciximab has not yet been replicated by specific small-molecule inhibitors of GP IIb/IIIa. Efforts are underway to understand the mechanisms by which abciximab may exert long-term inhibition of “clinical stenosis.”

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Synthetic Inhibitors of Platelet Glycoprotein IIb/IIIa in Clinical Development
Marc Verstraete

Circulation. 2000;101:e76-e80
doi: 10.1161/01.CIR.101.6.e76

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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