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Review

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Glycoprotein IIb/IIIa Inhibitors in Acute Coronary Syndromes: A new Paradigm in Cardiology

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Introduction

Acute coronary syndromes, namely, unstable angina and myocardial infarction, remain a major cause of morbidity and mortality (1). The light has been shed on the pathogenesis of these syndromes by recent developments, such as the increased use of coronary angiography in patients with acute coronary syndromes over the last two decades, a better understanding of platelet function and the coagulation pathways, and the development of advanced percutaneous techniques, percutaneous transluminal coronary angioplasty (PTCA) and coronary angioscopy.

The development and availability of the GPIIb/IIIa inhibitors has initiated a new era in our approach to these patients. Several studies are currently under way assessing the safety and usefulness of these compounds in the setting of percutaneous coronary interventions, acute coronary syndromes and in the secondary prevention of coronary artery disease. This review summarizes the current state of knowledge of the use of these inhibitors in the practice of cardiology.

Pathophysiology of Acute Coronary Syndromes

Unstable angina is defined as the evolving pattern of chest pain with multiple manifestations that are distinct from those of stable angina (2). Clinical and laboratory investigations have made it clear that the pathophysiology of unstable angina differs from that of stable angina. There is a loss of endothelial integrity, exposure of the subendothelial matrix and activation of the cellular components of the atherosclerotic plaque which eventually results in platelet activation and thrombus formation (2-5). Fitzgerald et al. assessed the indices of platelet activation in patients with stable and unstable coronary artery disease. To avoid the artifactual stimulation of platelets during venosection, they determined the urinary excretion of metabolites of thromboxane and prostacyclin (6). Significant platelet activation was demonstrated in patients with unstable angina and acute myocardial infarction, whereas no such activation was evident in patients with stable coronary artery disease. Furthermore, detailed histologic studies have demonstrated layers of platelet thrombi in different stages of organization at sites of coronary occlusion (4, 7). Platelet activation then leads to coronary occlusion either by obliterating the artery by thrombus or by causing coronary artery spasm by platelet derived vasoactive compounds (8). The same sequence of events could be responsible for complications of such as abrupt closure. Balloon angioplasty disrupts the continuity of the endothelium and exposes subendothelial substrates such as collagen, vWF, fibronectin, vitronectin and laminin. As in the acute coronary syndromes, this injury triggers platelet activation and thrombus formation.

As early as 1912, Herrick postulated that the triggering event of myocardial infarction was coronary thrombosis (9). DeWood proved Herrick's hypothesis by demonstrating angiographically that total occlusion of the coronary artery by a thrombus was present in

87% of patients evaluated within 4 hours of symptom onset (10). Plasminogen activation by thrombolytic treatment in these patients dissolves the fibrin elements of the thrombus and reestablishes the coronary patency (11).

Role of Platelets in Acute Coronary Syndromes

The therapeutic benefits of aspirin and/or thrombolytic agents after myocardial infarction lend support to the critical role of platelets and thrombus formation in the pathogenesis of acute coronary syndromes. Large scale clinical studies revealed that the early administration of thrombolytic agents was associated with significant reduction in mortality (12). Another intervention that conclusively demonstrated mortality benefit in patients with acute myocardial infarction was the administration of aspirin. A multicenter, multinational study, the Second International Study of Infarct Survival (ISIS-2) randomized 17.187 patients with acute myocardial infarction to receive 162.5 mg of oral aspirin daily for one month, or placebo (12). At 35 days, there were statistically significant, reductions in vascular mortality (23%) and reinfarction (55%) in the group receiving aspirin. Hence, drugs that dissolve thrombi, such as thrombolytic agents and/or drugs that prevent clot propagation, such as antiplatelet agents and/or anticoagulant agents, are widely used in acute coronary syndromes.

Currently, the proven benefit observed with aspirin administration in the setting of acute myocardial infarction would make it unethical to design placebo-controlled studies to investigate antiplatelet therapy. However, many patients have recurrent ischemic events despite being on aspirin therapy (13). Thus, an initially successful response to thrombolytic therapy may be countered by subsequent reocclusion (14). This has stimulated the search for the ideal adjunctive agent in attempts to inhibit coronary thrombus formation.

Platelet Adhesion and Aggregation

The processes of thrombosis and hemostasis are mediated via two distinct but complementary functions of platelets, namely adhesion and aggregation. Any discontinuity in endothelial cell coverage or exposure of the sub-endothelial matrix is met with rapid platelet adhesion to the vessel wall. Exposure the sub-endothelial substrates such as collagen, vWF, fibronectin, vitronectin and laminin is crucial in platelet adhesion. Adhesion causes platelet activation, which stimulates several intracellular pathways (15). Thromboxane A2, thrombin, norepinephrine, collagen, and adenosine diphosphate are some of the key players of these intracellular pathways (15,16). They act through different receptors to mobilize intracellular calcium mobilization and platelet degranulation (16,17). Platelets then release agonists of aggregation such as adenosine diphosphate, serotonin, and thromboxane A2; all of which activate surrounding platelets to form the platelet plug (15,16,17). Aspirin prevents platelet aggregation by reducing the synthesis of thromboxane A2, however platelet aggregation can still be initiated by other agonists, such as thrombin, subendothelial collagen, or, in the setting of PTCA, by stainless steel. In addition, aspirin inhibits the endothelial cell production of prostacyclin, a potent platelet inhibitor and vasodilator. Therefore, aspirin may not be the ideal antiplatelet agent in acute coronary syndromes.

Glycoprotein IIb/IIIa Receptor

Platelet functions such as adhesion or aggregation require recognition of a diverse number of proteins, including extracellular matrix proteins such as vWF, collagen, fibronectin, vitronectin and laminin. Thus, glycoprotein receptors on the platelet membrane are essential for normal platelet function.

Glycoprotein IIb/IIIa is the most prevalent protein on the platelet surface (18). There are approximately 50,000 molecules on the surface of unactivated platelets. It is a member of the integrin family of the adhesion receptors (19). The integrins are a family of receptors that mediate many cell-to-cell and cell-to-matrix interactions. All integrins are heterodimers of α and β subunits. GPIIb/IIIa is present only on the surface of platelets and cells of megakaryocyte lineage (18). It is a heterodimer subunit composed of α_{IIb} and β_3 subunits (Figure 1) (19).

If the extracellular matrix becomes exposed by disruption of the overlying endothelial cells, platelets may attach to the exposed areas. This attachment makes the platelets more adhesive by inside-out activation of the GPIIb/IIIa receptor on the platelet surface (19). The integrin then captures circulating molecules like fibrinogen or von Willebrand Factor that subsequently form bridges linking the platelets and the matrix (Figure 2). Interestingly, several studies revealed that the concentration of circulating fibrinogen is a potent risk factor for acute coronary syndrome, suggesting a critical role for fibrinogen in the pathogenesis of acute coronary syndromes (20). Additional studies have linked ex vivo platelet reactivity to outcome in patients who have suffered a myocardial infarction (21).

Glanzman's thrombasthenia is an inherited abnormality in GPIIb/IIIa expression or function that impairs platelet aggregation and results in a bleeding disorder. This disorder formed the "knock-out" model for the early research with this receptor. Marjorie Zucker studied the platelets of a young male patient with Glanzman thrombasthenia almost three decades ago (22). Tests of coagulation were normal, the bleeding time was > 15 minutes, and there was no clot retraction in whole blood at 1 hour. She also observed that the patient's platelets were severely deficient in fibrinogen. This led to the conclusion that fibrinogen binding is critical for platelet aggregation. Recent studies demonstrated that platelet aggregation requires the binding of fibrinogen and von Willebrand factor to the receptor, GP IIb/IIIa, on the platelet surface (Figure 2) (18).

Clinical observations have demonstrated that spontaneous, severe bleeding is uncommon among patients with thrombasthenia (23). Minor bleeding events such as purpura, epistaxis and gingival hemorrhage are almost constant features of this disease; however, with supportive care the prognosis is usually excellent (23). Unlike hemophilia, the severity of bleeding in thrombasthenia does not correlate with the severity of the platelet GP IIb/IIIa abnormality. The measurements of GP IIb/IIIa in thrombasthenic patients have revealed that some patients with nearly absent GP IIb/IIIa have minimal bleeding complications, and some patients with substantial amounts of GP IIb/IIIa can present with recurrent and severe bleeding (23). It has been suggested that cells other than megakaryocytes and platelets may be abnormal in Glanzman's thrombasthenia, as the GP IIIa component of the integrin receptor is present in many tissues as the β subunit of the vitronectin receptor. This could be the basis for variability in bleeding symptoms among thrombasthenic patients. These clinical observations provided insight stimulating the development of GP IIb/IIIa receptor as a therapeutic target in patients with coronary artery disease.

Early onset coronary artery disease is a polygenic disease, which progresses through the interaction between the effects of multiple genes and several environmental factors. Recently, Weiss et al reported a high frequency of a particular polymorphism, PlA2, of the gene encoding glycoprotein IIIa in kindreds with a high prevalence of premature myocardial infarction (24). Furthermore, the same researchers observed a strong association between the PlA2 polymorphism of

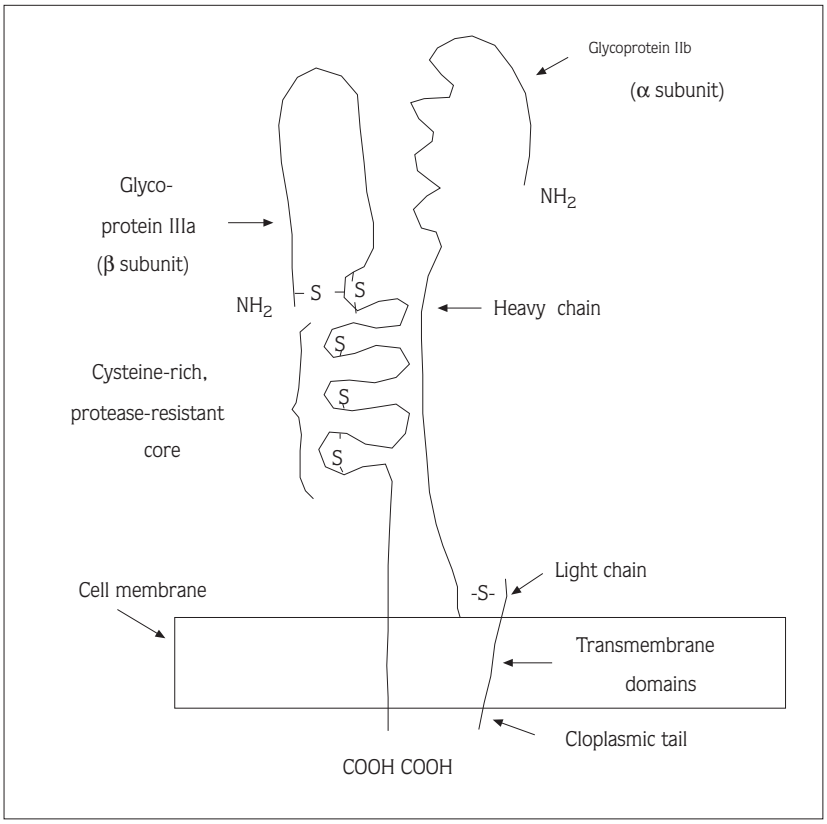

Figure 1. Chemical structure of the platelet glycoprotein IIb/ IIIa receptor is shown.The α and β subunits are noncovalently bound to each other. (From Lefkovitz J, Plow EF, Topol EJ. Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. N Eng J Med 1995,332:1153-1559. Reproduced by permission).

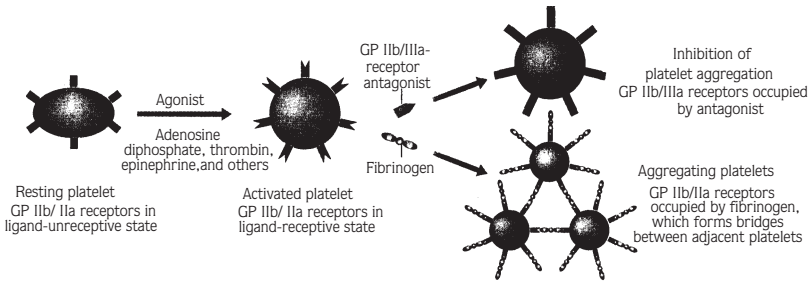

Figure 2. Processes of platelet activation and aggregation. Inhibitors of glycoprotein IIb/IIIa receptors block the binding of fibrinogen to the IIb/IIIa receptor. (From Lefkovitz J, Plow EF, Topol EJ. Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. N Eng J Med 1995;332:1153-1559. Reproduced by permission).

the GP IIIa gene and coronary thrombosis. This association was strongest in people who had suffered coronary events before the age of 60. A report published in *The Lancet* entitled "Clues to the death of an Olympic champion" linked this polymorphism to the death of Sergei Grinkov, aged 28, two-time Olympic skating gold medalist who collapsed suddenly while training on the ice-rink (25).

Glycoprotein IIb/IIIa Antagonists

Agonists of platelet aggregation, such as adenosine diphosphate, serotonin, and thromboxane A2, activate adjacent platelets to form the platelet plug(15,16, 17). Irrespective of the agonist, the final common pathway leading to the platelet activation is mediated by the binding of fibrinogen to the GP IIb/IIIa receptor (26,27). Platelet activation from any mechanism results in a conformational change in the GPIIb/ IIIa receptor that enables binding of the cognate ligand, fibrinogen. This universal role of the GPIIb/IIIa receptor has made it a potential therapeutic target in acute coronary syndromes. In particular, it raises the possibility that the blocking of this receptor by an antibody could completely prevent the final common pathway of platelet aggregation.

Using fibrinogen-coated beads as a screening assay, Coller et al. were able to develop monoclonal antibodies that blocked the interaction of platelets with fibrinogen (28). This seminal finding led to the development of several inhibitors of this receptor. These agents can be classified as competitive and non-competitive inhibitors of fibringen binding, depending on their pharmacokinetics and pharmacodynamics. The F(ab) fragment of the human-murine chimeric antibody (c7E3) is the only non-competitive inhibitor of fibrinogen binding currently available. As originally developed, the monoclonal antibody 7E3 was entirely murine in composition. However, strong immunogenecity with the murine antibody and severe thrombocytopenia with the human antibody lead to the development of genetically engineered chimeric monoclonal c7E3 Fab, which has 75% human and 25% murine composition. It occupies the GPIIb/IIIa receptor permanently. It has an extended half-life, which may be advantageous in the long-term. In addition to the affinity on α_{IIb} β_3 (GP IIb/IIIa), c7E3 also block vitronectin receptors, which are known to stimulate smooth muscle cell proliferation and migration (29). These properties make this agent more appealing to the interventional cardiologist, as smooth muscle cells are vital in the processes of restenosis after a percutaneous coronary intervention. The reversal of the effects of cE73 in cases of an adverse effect such as bleeding can occur only by externalization of new receptors on the platelet surface or by supplying new platelets either from the bone marrow or externally by platelet transfusion.

There are several competitive inhibitors of GPIIb/ IIIa receptor being developed, including a cyclic peptide agent (Integrelin), the non-peptide mimetic (tirofiban), and orally active agents such as (xemilofiban) (Figure 3). The binding of the competitive inhibitors to the integrin receptor is concentration-dependent and reversible (30). Thus, anti-platelet effects are directly related to the duration of the infusion and can be readily reversed by stopping the infusion. Shortened biological half-life of competitive inhibitors may prevent severe bleeding complications and improve the safety profile.

Use of GPIIb/IIIa in the Setting of Percutaneous Coronary İntervention

Acute or abrupt closure of dilated vessel after percutaneous transluminal coronary angioplasty (PTCA) occurs in 2-8% of patients (31,32), and is responsible for virtually all serious in-hospital morbidity and mortality after PTCA. The pathophysiologic mechanisms of acute coronary artery occlusion after successful PTCA are probably multifactorial and involve platelet activation and thrombus formation following disruption of

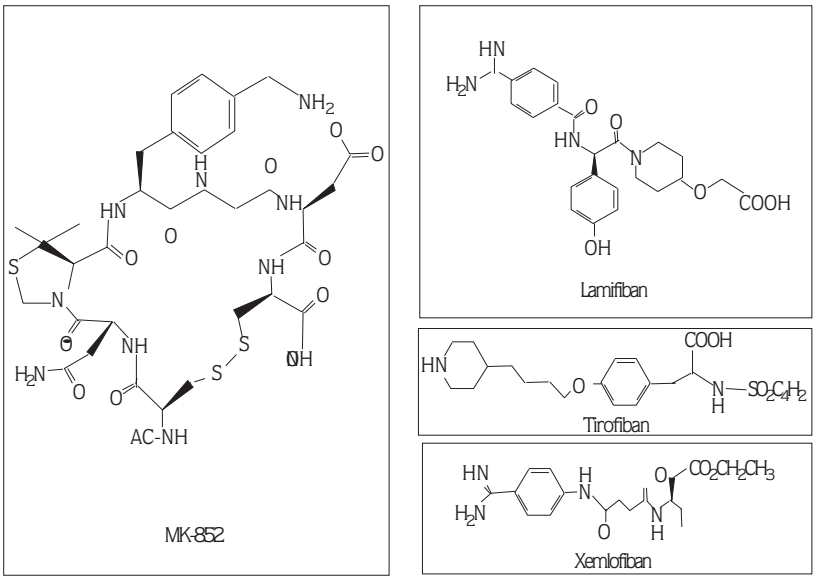

Figure 3. Chemical structure of some inhibitors of platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. N Eng J Med 1995;332:1153-1559. Reproduced by permission).

the endothelial layer by balloon and exposure of the extracellular matrix to the platelets. The same sequence of events occurs in acute coronary syndromes following natural rupture of the unstable lipid-rich plaque. Starting from this paradigm, several large trials were conducted that assessed the utility of GPIIb/IIIa inhibitors after coronary intervention.

Four large trials, using three different agents, have been published within the past two years: ; the Evaluation of c7E3 In Preventing Ischemic Complications (EPIC) (33) and the Evaluation of PTCA to Improve Long-term Outcome by c7E3 (EPILOG) both using the antibody fragment abciximab (ReoPro) (34); the Integrilin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis II (IMPACT II) trial evaluating the peptide Integrilin (35); and the Randomized Efficacy Study of Trofiban for Outcomes and Restenosis (RESTORE) using the non-peptide mimetic trofiban (Aggrastat) (36) (Table 1).

Table 1. Phase III Clinical Trials Evaluating Glycoprotein IIb/IIIa Inhibitors after Coronary Intervention

Trial	Agent	Sample Size
Epic	c7E3 Fab	2099
Epilog	c7E3 Fab	2792
Impact II	Integrelin	4010
Restore	Tirofiban	2500

The first GPIIb/IIIa antagonist tested in the setting of percutaneous coronary intervention was abciximab in the EPIC study. Nearly 2100 patients were randomized after percutaneous transluminal coronary angioplasty to receive placebo, a bolus of abciximab, or an identical bolus of abciximab followed by a 12 hour infusion. The bolus dose of abciximab was started at least 10 minutes before the procedure and given over a 5 minute period. All patients were also treated with aspirin and heparin. Heparin was given intravenously in an initial bolus dose of 10.000 to 12.000 units. Activated clotting time was maintained at 300 to 350 seconds during the procedure. A 35% reduction in the ischemic endpoints (which included a composite of death, nonfatal myocardial infarction, and repeat revascularization) at 30 days was noted after the use of abciximab bolus and infusion. The benefit largely persisted at 6 months with a 23% reduction in the same endpoints (33). However, this benefit was at the expense of a doubling of bleeding rates.

To further explore the optimal dosing strategy of heparin in the setting of c7E3 administration, another prospective, double-blind trial, EPILOG, randomly assigned patients undergoing percutaneous coronary revascularization at 69 centers to receive abciximab with standard-dose heparin (initial dose of 100 U per kilogram of body weight), abciximab with low dose heparin (initial dose of 70 U per kilogram of body weight), or placebo with standard-dose heparin. The end points were death from any cause, myocardial infarction, or urgent revascularization. The Safety and Efficacy Monitoring Committee recommended stopping the study

after the enrollment of only 2792 of the planned 4800 subjects in view of the finding at interim analysis of a significant reduction in primary-outcome combined endpoints of death and myocardial infarction in the treatment arms (5.2% versus 11.7% in the placebo group) (34). There were no significant differences among the groups in the risk of major bleeding, although minor bleeding was more common among groups receiving abciximab with standard dose heparin. This benefit persisted at the 6th month of follow-up. Similar benefit and safety profiles were observed at 2 days with competitive inhibitors in IMPACT II (Integrelin) and RESTORE (Tirofiban) trials; however, by the 30th day there was a significant loss in the reduction of ischemic endpoints (35, 36). The loss of long-term benefit may be related to the short biological half-lives of these agents, or to their more specific effects on the GP IIb/IIIa receptor rather than on the vitronectin receptor.

These results suggest that each GPIIb/IIIa inhibitor possesses specific advantages and disadvantages. Abciximab has, in addition to a long biological half-life, a crossreactivity with other receptors, including vitronectin and MAC-1. These receptors may play a key role in the processes of restenosis after coronary intervention (29). On the other hand, the short elimination half-life of competitive inhibitors may improve their safety profile and decrease the incidence of severe bleeding complications after the use of these agents.

In summary, these trials have shown that the blockade of platelet glycoprotein IIb/IIIa receptor can reduce ischemic complications after percutaneous coronary intervention.

Use of GPIIb/IIIa in The Setting of Unstable Angına

As with abrupt closure after coronary intervention, platelet aggregation is the key event in acute coronary syndromes. Therefore, one might expect a similar improvement in outcome with GP IIb/IIIa blockade in the setting of acute coronary syndromes. However, less is known about the role of these agents in unstable angina and/or acute myocardial infarction.

Several large-scale trials have evaluated this new therapy in patients with unstable angina. The results of the CAPTURE study (Chimeric 7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment) were announced in 1995. The study was designed as a placebo controlled study of c7E3 Fab in 1400 patients with refractory unstable angina scheduled for percutaneous coronary intervention in 75 clinical centers in Europe, Israel, and Canada (37). In this large trial, patients were treated with a bolus (0.25mg/kg) plus an infusion (10µg/min) of c7E3 Fab, beginning 18 to 24 hours before the PTCA, and continuing through 1 hour following PTCA. The Safety and Efficacy Monitoring Committee recommended stopping the study after enrollment of 1050 subjects in view of a significant reduction in the primary clinical composite endpoints of the trial: death, myocardial infarction or need for urgent intervention (11.3% versus 15.9% in the placebo group). Major bleeding was uncommon, but occurred more often with abciximab than with placebo (3.8% versus 1.9%). Using the same agent, van den Brand et al. reported an improved clinical course in the coronary lesion morphology in patients with unstable angina who were refractory to medical treatment (38). Sixty patients were randomized to c7E3 or placebo after initial angiography had demonstrated a culprit lesion amenable to angioplasty. After administration by bolus and infusion of c7E3, angiography was repeated and angioplasty was performed. Major events, defined as death, MI and urgent intervention, were reduced in the c7E3 group (P=0.03). Quantitative angiography showed an improvement in the percentage luminal diameter and the resolution of intracoronary thrombi as well as an improvement in TIMI flow grade in the c7E3 group.

Theroux et al. published their observations with lamifiban, a nonpeptide, competitive GP IIb/IIIa inhibitor (39). In this prospective, dose-ranging, double-blind study, 365 patients with unstable angina were randomized to an infusion of 1, 2, 4, or 5 mg/minute of lamifiban for 72 to 120 hours, or to placebo. All doses of lamifiban-protected patients with unstable angina from severe ischemic events during a 3-to 5-day infusion, and reduced the incidence of death and infarction at 1 month (2.5% versus 8.1% in the placebo group). Schulman et al. reported that integrelin, another competitive inhibitor of GPIIb/IIIa, reduced the number and duration of ischemic events detected during Holter monitoring (8.41 + 5.29 minutes versus 26.2 + 9.8 minutes over 24 hours) in patients with unstable angina pectoris when compared with aspirin and standard anti-ischemic treatment (40).

Future trials will hopefully shed more light on the potential role of glycoprotein IIb/IIIa blockade in the setting of unstable angina.

Use of GPIIb/IIIa in the Setting of Acute Myocardial Infarction

The usual cause of myocardial infarction in humans is an occlusive thrombus in the coronary artery (9). Over the last decade, the effective use of thrombolytic therapy has started a new era in the treatment of this major cause of morbidity and mortality. Appropriate administration of thrombolytic therapy to patients with acute myocardial infarction is associated with a reduction in mortality (12). The success of thrombolytic therapy stems from its ability to activate plasminogen, lyse the occlusive thrombus, and restore the blood flow in 70% of the infarct-related arteries (41). However, about 30% of occluded infarct related arteries still cannot be reperfused even with the best available regimen of thrombolytic therapy. Additionally, in the initial trials assessing thrombolytic therapy, the incidence of coronary occlusion from rethrombosis was approximately 20%, and the incidence of reinfarction was 10% (42). Most of these occlusions occurred in the first 24 hours. One plausible cause of resistance to thrombolytic therapy is the presence of platelet-rich thrombus. Platelets are the richest source of circulating plasminogen activator inhibitor (PAI-1), diminishing the effectiveness of exogenously administered plasminogen activators (streptokinase or t-PA). Patients who undergo coronary thrombolysis with either streptokinase (43) or t-PA (44) exhibit an increase in their urinary excretion of metabolites of thromboxane, consistent with the activation of platelets by these thrombolytic agents. The therapeutic benefit of combined antiplatelet therapy with thrombolytic therapy was strongly demonstrated in the ISIS-2 study, where the combination resulted in a doubling in the reduction of mortality that was observed in patients treated with either aspirin or streptokinase alone (12). In a chronic, canine model of coronary thrombosis, Fitzgerald et al. demonstrated that tPA 10 mg/kg/min induced reperfusion in 55 ± 7 minutes, but was associated with complete reocclusion in 9/10 animals. Reocclusion was prevented by the combination of t-PA and c7E3 (45). Therefore, the use of GP IIb/IIIa inhibitors along with thrombolytic therapy may potentially improve patency of infarct vessels, reduce vessel closure, and the incidence of reinfarction. Gold et al. administered c7E3 Fab to patients who had angiographic occlusion of infarct-related artery in the setting of acute anterior myocardial infarction (46). GP IIb/IIIa blockade resulted in normal blood flow at the infarct-related artery without any further intervention in 7 out of 13 patients. c7E3 Fab antibody also suppressed the expression of PAI-1 by cultured microvascular cells (47); therefore, this antibody may have a beneficial effect on the fibrinolytic balance of t-PA:PAI-1 along with the well known anti-platelet effects.

The first large-scale phase III trial of these agents after myocardial infarction is the PARADIGM study. This study will evaluate the use of competitive, non-peptide inhibitor lamifiban in combination with front-loaded t-PA after myocardial infarction. ASSENT-II, HERO-II, SPEED, GUSTO 4, APPLAUD and SYMPHONY are some of the other acronyms for other large-scale studies that will prospectively assess these novel agents in the setting of acute myocardial infarction (30).

Conclusions

GP IIb/IIIa receptor-based therapy has the potential for a broad application in acute coronary syndromes and percutaneous coronary interventions. The risk of bleeding can be minimized by adjusting the adjunctive treatments, as shown in the EPILOG trial (34). However, there are still unresolved issues related to the use of these agents. Additional studies are needed to better define the patient selection criteria, optimum dosing and duration strategies, hospital costs and long-term outcome. Another recent breakthrough in this area has been the development of oral GP IIb/IIIa blockers, which have the potential for long-term administration for the secondary prevention of coronary artery disease. Large phase II and III trials are currently under way to evaluate the role of long-term inhibition with these oral agents. The high economic costs of these pharmaceutical agents will unfortunately be a major limiting factor in the wider use of these therapies. Further cost-benefit analysis may help us to understand the economics of glycoprotein IIb/IIIa blockade therapy in different clinical settings.

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