

Glycoprotein IIb/IIIa Platelet Receptor Inhibitors: A New Dimension in Cardiology

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Abstract

Platelets play a key role in the pathogenesis of atherosclerosis, acute coronary syndromes and ischaemic complications following percutaneous coronary intervention. More recently, the platelet glycoprotein (GP) IIb/IIIa receptor has been identified as the pivotal mediator of platelet aggregation, leading to thrombus formation. This has led to the emergence of a novel class of potent antiplatelet agent, the GP IIb/IIIa receptor antagonists. These agents show great promise in reducing ischaemic complications of coronary angioplasty and acute coronary syndromes. This review summarizes the current state of knowledge of the biology of GP IIb/IIIa receptor, the different classes of GP IIb/IIIa receptor antagonists, the results of the various trials, and their impact on current clinical practice.

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Introduction

Recent data have implicated that platelet activation and aggregation are important in the pathogenesis of atherosclerosis, acute coronary syndromes and in ischaemic complications following percutaneous interventions.^{1,2} Platelet thrombus is also believed to be a key component in the process of restenosis after angioplasty.³

The recognition of the role of platelets in these conditions has prompted development of a variety of pharmacologic agents to target platelet activation and aggregation. Of particular importance is the recent discovery of a new class of antiplatelet agents, the glycoprotein (GP) IIb/IIIa antagonists. Their profound impact on reducing ischaemic complications has dramatically improved the management of patients undergoing percutaneous revascularization and those with acute coronary syndromes.

Integrins

The glycoprotein receptors belong to a family of transmembrane proteins known as integrins which consist of heterodimeric molecules made up of α and β subunits held together by noncovalent bonds. Twelve α -subunits and eight β -subunits have so far been identified. Various combinations of these subunits form receptors with different affinities for ligands, including fibrinogen, fibronectin, vitronectin, von Willebrand factor, thrombospondin and collagen.⁴⁻⁶ Glycoprotein IIb/IIIa, the prototypic receptor, was the first integrin to be

identified. Glycoprotein IIb is a typical α integrin subunit and GPIIIa is a typical β subunit. This model was used for subsequent characterization of the other integrins. Glycoprotein IIb/IIIa receptors are platelet-specific and uniquely adapted to platelet function. Coded by separate genes on the long arm of chromosome 17, the two subunits of GP IIb/IIIa are assembled on megakaryocytes for final expression.

Molecular Biology of Platelets in Thrombosis and Restenosis

Thrombus formation is initiated at the site of arterial injury whenever endothelial integrity is disrupted and subendothelial matrix is exposed. The first step in haemostasis involves the passive adhesion of platelets to exposed collagen and von Willebrand factor. This is mediated by specific receptors, glycoproteins Ib and Ia/IIa. Following adhesion, one of any number of agonists may activate the platelets. These include collagen in the subendothelium, adenosine diphosphate, thromboxane A₂, thrombin, epinephrine and serotonin.

At least three different processes occur with platelet activation. First, there is degranulation of platelets with release of chemical mediators including thrombin, serotonin, and adenosine diphosphate (ADP). This further stimulates nearby platelets and recruits additional platelets to the site of injury. Second, thromboxane A₂, another potent platelet agonist, is produced via arachidonic acid metabolism. Third, a structural change occurs on the surface of the platelets facilitating the forma-

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tion of prothrombinase complexes and amplifying thrombin generation. Thrombin appears to be the most important platelet agonist. It activates platelets, converts fibrinogen to fibrin and amplifies its own generation.

Several other effects also occur with platelet activation. Activated platelets undergo conformational changes from an ovoid or discoid shape to one with pseudopods, leading to a dramatic increase in cell surface area and converting GP IIb/IIIa receptors from a ligand non-receptive to ligand receptive state. This leads to the final step in haemostasis, platelet aggregation which is mediated by GP IIb/IIIa, the most abundant of the integrin receptors.

There are approximately 50 000 to 80 000 GP IIb/IIIa receptors on each platelet.⁵ These receptors have a high affinity for the peptide sequence arginine-glycine-aspartic acid (RGD), a sequence found in fibrinogen, von Willebrand factor, fibronectin and vitronectin. All of these ligands contain only one RGD sequence except fibrinogen, which has two RGD sequences. Fibrinogen is the preferred ligand because of its high concentration in the plasma. Being a bivalent dimer, fibrinogen is able to crosslink adjacent platelets; thus GP IIb/IIIa binding of fibrinogen constitutes the “final pathway” of platelet aggregation leading to thrombus formation (Fig. 1). Other adhesive glycoproteins such as fibronectin, vitronectin, and von Willebrand factor are also capable of binding to GP IIb/IIIa receptors. This may be important in platelet adhesion to subendothelial proteins.⁴⁻⁷

Activated platelets have also been implicated in the pathogenesis of restenosis following percutaneous coronary intervention. Platelets can cause transformation of smooth muscle cells in the vessel media from a contractile to a secretory phenotype via the release of intracellular cytokines and growth factors. Left unchecked, neointimal hyperplasia, wherein smooth muscle cells migrate to the intima, proliferate and secrete extracellular matrix, can lead to restenosis.⁸ The use of GP IIb/IIIa antagonists may favourably alter the restenosis process by limiting platelet-dependent thrombosis at the site of

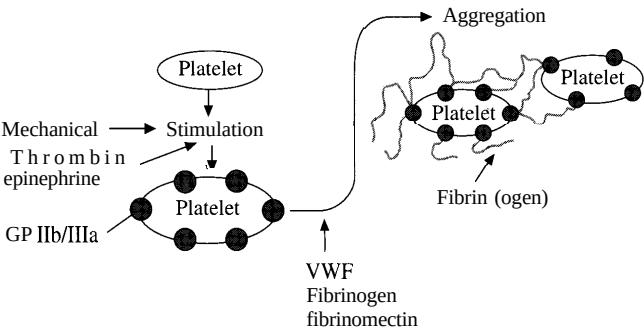


Fig. 1. Physiology of platelet aggregation.

vascular injury caused by percutaneous intervention.

Glanzmann Thrombasthenia

Much of the understanding of the biological effects of platelet GP IIb/IIIa blockade were derived from the study of hereditary haematological disorder, Glanzmann thrombasthenia. In this condition, first described in 1918, patients are found to have a congenital absence of functioning GP IIa/IIIa receptors.^{10,11} Platelets of these patients fail to aggregate in response to all known agonists including ADP, serotonin and thrombin. Without functioning GP IIb/IIIa, the bleeding time is profoundly prolonged. These patients have serious frequent episodes of mucocutaneous bleeding although spontaneous major haemorrhages involving the gastrointestinal or central nervous systems are rare. This disorder provided the model for development of agents that could block GP IIa/IIIb receptors. The clinical effect of these agents would be to inhibit fibrinogen’s ability to bind to GP IIb/IIIa receptors and prevent thrombosis mediated by platelet-fibrinogen interaction following atherosclerotic plaque rupture.

Classification of GP IIb/IIIa Antagonists

While no formal classification exists, there are several different classes of GP IIb/IIIa inhibitors, distinguishable by their pharmacokinetics, immunogenicity, therapeutic efficacy and safety profiles (Table I). This include the monoclonal antibodies, naturally occurring disintegrins and synthetic GP IIb/IIIa inhibitors.

Monoclonal Antibodies to GP IIb/IIIa

Coller¹² was the first to develop the murine antibody against the GP IIb/IIIa integrin. It was created by injecting mice with whole human platelets and then isolating a cell line producing an antibody to GP IIb/IIIa. The

TABLE I: CLASSIFICATION OF GP IIb/IIIa ANTAGONISTS

Monoclonal antibodies
Chimeric human-murine monoclonal antibody (c7E3 Fab, abciximab, ReoPro®)
Natural GP IIb/IIIa antagonists (disintegrins)
Snake venoms
RGD-dependent (trigramin, bitistatin, kistrin)
KGD-dependent (barbourin)
Synthetic GP IIb/IIIa antagonists
Peptides
Cyclic RGD peptide - DMP 728
Cyclic KGD peptide - Integrilin™
Nonpeptides
Tetrafibricin
Tirofiban
Lamifiban
Oral GP IIb/IIIa antagonists
Xemilofiban
Orbofiban
RPR 109891

lymphocytes were then fused with an "immortal" malignant cell line to produce large quantities of identical monoclonal antibodies with an absolute specificity for a single protein epitope. The Coller antibody exhibits high affinity and specificity for GP IIb/IIIa receptor, making it an ideal potent antiplatelet agent. The original murine immunoglobulin was further modified and cleaved into fragments m7E3 F(ab')₂, with most of the Fc region eliminated. This is to avoid the potential for complement activation and minimises the development of thrombocytopenia due to rapid clearance of antibody-coated platelets in the spleen and reticuloendothelial system. To further reduce the immunogenicity, the DNA sequences coding for the constant domains of the Fab murine monoclonal antibody were replaced by the corresponding human immunoglobulin constant region sequences,¹³ resulting in the final chimeric human-murine c7E3 Fab fragment (abciximab, ReoPro®, Eli Lilly, Indianapolis, IN). This agent blocks the GP IIb/IIIa receptor and prevents the binding of fibrinogen.

Initial studies using various animal models have shown that m7E3 F(ab')₂ can prevent thrombosis in a stenosed arterial segment¹⁴ and minimize cyclic flow variation." Pretreatment with c7E3 can further accelerate reperfusion when used in conjunction with a thrombolytic agent¹⁶ and prevent coronary artery reocclusion.¹⁷ Histologically, c7E3-treated blood vessels show only a single monolayer of platelets despite the presence of underlying extensive vascular damage. This represents a process of "passivation" in which an arterial surface that normally would support platelet deposition is transformed into one that will no longer do so. It may explain the reason for the sustained benefits seen following initial short-term treatment with c7E3 Fab. These experimental findings helped form the theoretical basis for the use of this drug in subsequent human clinical trials.

It has been observed in animal studies that to prevent thrombus formation, more than 80% of GP IIb/IIIa integrin blockade is required to reduce ADP-induced platelet aggregation to <20% below baseline.^{16,17} Tcheng et al¹⁸ showed that a bolus dose of 0.25 mg/kg of c7E3 Fab in humans achieved this same level of receptor blockade and produced consistent effective platelet inhibition. Further increases in the bolus dosing beyond 0.25 mg/kg did not produce an incremental inhibitory effect on platelet aggregation. This antiplatelet effect was maintained by an infusion of c7E3 Fab at 10 µg/min for up to 12 hours. Upon cessation of infusion, normal haemostasis returned within 12 hours. Free plasma c7E3 Fab is cleared rapidly from the circulation although platelet-bound drug persisted for several days.

Naturally Occurring GP IIb/IIIa Antagonists: Disintegrins

There are several naturally existing peptides which have intrinsic activity against GP IIb/IIIa. One of these

include peptides derived from snake venoms, collectively termed the "disintegrins". These peptides share RGD sequence that are homologous with endogenous adhesive proteins such as fibrinogen and von Willebrand factor. Most of these natural peptides are not suitable for human use as therapeutic agents because of their high immunogenicity. They nonetheless have provided excellent templates for the design of synthetic platelet antagonists. An example is the disintegrin barbourin, isolated from the pygmy rattle snake *Sistrurus M barbouri*, which has an increased specificity compared with other disintegrins for GP IIb/IIIa.¹⁹ The specificity is a result of a single substitution of arginine for lysine and has become the model for development of synthetic peptide GP IIb/IIIa inhibitors such as integrilin. In addition, analysis of the disintegrins has shown that cyclic peptides are more potent and stable because of their resistance to enzymatic breakdown. Synthetic linear peptides based on RGD sequences have low potency and poor stability in the plasma.²⁰

Synthetic Peptide and Non-peptide Antagonists

The synthetic GP IIb/IIIa antagonists include a heterogeneous mix of peptide and non-peptide mimetics, all with specificity for GP IIb/IIIa. The design goals have been to create an agent with a high selectivity for the GP IIb/IIIa integrin while reducing the potential for bleeding, cross reactivity with other closely related integrin receptors and immunogenicity. The synthetic peptides typically contain either RGD or KGD binding sequences. When synthesized in a cyclical configuration, these peptides become more stable in plasma and exhibit higher affinity for integrin receptors. The prototypic cyclic RGD analog is DMP 728 (DuPont Merck Pharmaceutical, Wilmington, Delaware) and the cyclic peptide antagonist based on KGD sequence is integrilin (COR Therapeutics, South San Francisco, California). These antagonists are intravenous preparations.

The non-peptide synthetic antagonists mimic the spatial and charge conformations of the RGD binding sequence. Agents being developed include tetrafibricin, tirofiban (Merck, West Point, Pennsylvania) and lamifiban (RO 44-9883, Hoffman-LaRoche, Basel, Switzerland). Another approach, embodied by the development of the oral GP IIb/IIIa antagonistic agents, provides the potential for long-term platelet inhibition and the prevention of future thrombotic events. Xemlofiban (SC-54684, Searle, Skokie, Illinois) is the orally active nonpeptide antagonist prototype developed. Approximately ten other oral agents are in various stages of development.

Role of GP IIb/IIIa Antagonists in Percutaneous Intervention

Although percutaneous coronary intervention is associated with improvement in symptom of ischaemia and

quality of life, it is beset with the problem of abrupt closure in 4.4% to 8.3% of cases.²¹ Aspirin significantly reduces the risk of abrupt closure and acute myocardial infarction in patients undergoing angioplasty but its antiplatelet effect remains relatively weak. Ischaemic complications continue to occur in 10% to 20% of patients who receive aspirin. Experimental studies have shown that approximately 70% of platelet deposition at the site of balloon injury is GP IIb/IIIa dependent while the remaining 30% is from non-GP IIb/IIIa-mediated platelet subendothelial adhesion.^{22,23} As injury with coronary intervention is both predictable and obligatory, this area was the first investigated in human clinical trials of c7E3 Fab and other GP IIb/IIIa inhibitors.

Tcheng et al¹⁸ were the first to evaluate the safety of c7E3 Fab as a prophylactic adjunct in high-risk PTCA. He found that administration of c7E3 Fab at a dose of 0.25 mg/kg resulted in more than 80% of platelet GP IIb/IIIa integrin blockade with platelet aggregation suppressed to less than 20% of baseline. This provided the pharmacologic basis for subsequent large-scale clinical trials.

The clinical efficacy of c7E3 Fab in percutaneous interventional procedures was fully established in the landmark EPIC trial (Evaluation of c7E3 for the Prevention of Ischemic Complications).²⁴ In this study, 2099 patients undergoing high-risk coronary angioplasty at 56 centres were randomised to placebo, a bolus of c7E3 Fab (0.25 mg/kg) or a bolus of c7E3 Fab (0.25 mg/kg) followed by a 12-hour c7E3 Fab infusion (10 µg/min) prior to the procedure. High-risk patients as defined in the study included those sustaining an acute myocardial infarction, presenting with unstable angina or having unfavourable coronary anatomy. All patients received aspirin (325 mg) and heparin (10 000 to 12 000 IU bolus) to achieve an activated clotting time of 350 seconds prior to the procedure. The primary endpoint of the study was the composite rate at 30 days of death, non-fatal myocardial infarction, unplanned surgical revascularization, unplanned repeat percutaneous procedure, or insertion of an intra-aortic balloon pump for refractory ischaemia. There was a highly significant 35% risk reduction in the composite-event rates in patients who received the administration of bolus and infusion of c7E3 Fab compared to placebo. In patients who received only bolus c7E3 Fab, there was still a 10% risk reduction in the occurrence of the primary endpoint. The principal beneficial effect was in the reduction of myocardial infarction following percutaneous intervention, though the effect on all components of the composite was consistent, favouring bolus and infusion of c7E3 Fab.

Notably, c7E3 Fab was particularly effective in the unstable clinical syndromes (acute myocardial infarction and unstable angina).²⁵ c7E3 Fab reduced the ischaemic event rates at 30 days by 83% and 70% in patients

with acute myocardial infarction treated within 12 hours of symptom onset and refractory unstable angina respectively. In a subgroup analysis of 66 patients undergoing primary or rescue angioplasty, none had reinfarction (0% versus 8.7% placebo) or urgent intervention at 30 days (0% versus 17%) when given bolus and infusion of c7E3 Fab. Only 4.5% of actively-treated patients experienced adverse events compared to 47.8% of placebo-treated patients ($P = 0.002$). These convincing results contributed to the eventual approval by the Food and Drug Administration (FDA), on 22 December 1994, of c7E3 Fab for adjunctive use in high-risk coronary intervention.

In addition to the 30-day efficacy, the benefit of c7E3 Fab bolus and infusion was sustained at six months. Follow-up of EPIC patients showed a reduced incidence of major ischaemic events (death, myocardial infarction, and urgent revascularisation) in patients receiving bolus/infusion of c7E3 Fab compared to placebo (27.0% versus 35.1%; 23% reduction, $P = 0.001$).²⁶ This was driven primarily by the reduced need for repeat target vessel revascularisation in c7E3 Fab-treated patients (16.5% versus 22.3%; 26% reduction, $P = 0.007$) suggesting an effect on clinical restenosis.

Therapeutic use of c7E3 Fab in percutaneous interventions has a tradeoff; there is an increased risk of bleeding complications with a doubling of major bleeding and need for blood product transfusion (14% versus 6.6% in placebo-treated patients, $P = 0.001$) in c7E3 Fab-treated patients in the EPIC trial.²⁷ Most bleeding was associated with the vascular puncture site. Bleeding increased the procedural morbidity, prolonged length of hospitalization and necessitated more frequent blood transfusion. Spontaneous major organ complications, mainly haemetemesis and gross haematuria, occurred rarely (1.3%). Importantly, the risk of stroke was not increased with the use of c7E3 Fab. Further analyses revealed that bleeding was inversely related to weight, being highest in the lightest weight tertile (76.8 kg) and lowest in the heaviest tertile (>89.9 kg). As heparin dosing was not weight-adjusted in the EPIC study, the question has been raised whether the risk of bleeding may be reduced with more appropriate heparin dose reduction and other patient management guidelines.

The EPILOG trial (Evaluation of PTCA to Improve Long-term Outcomes by c7E3 GP IIb/IIIa receptor blockade), a follow-up study to EPIC, sought to extend the EPIC observations to all patients and address the bleeding concerns. In EPILOG, patients undergoing non-high-risk angioplasty were randomised into three arms: bolus and infusion of weight-adjusted c7E3 Fab and standard-dose weight-adjusted heparin (100 U/kg bolus with additional doses to achieve an ACT >300 seconds), bolus and infusion of weight-adjusted c7E3 Fab with low-dose weight-adjusted heparin (70 U/kg bolus

with additional doses to achieve an ACT of 225 to 300 seconds); bolus and infusion of placebo and standard-dose weight-adjusted heparin. An interim analysis of the first 1500 patients documented a 68% reduction in death and myocardial infarction in those who received c7E3 Fab, leading to early termination of EPILOG for efficacy.²⁸ Importantly, the risk of bleeding complications was also reduced in those administered low-dose weight-adjusted heparin and c7E3 Fab. There was an observed doubling of efficacy of c7E3 Fab in this trial compared to EPIC. This is attributed to the fact that more patients were able to receive the full dose of the c7E3 Fab treatment without premature termination from bleeding complication.²⁹

The benefit of c7E3 Fab in PTCA was further established by the results of the CAPTURE trial (Chimeric 7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment). In this trial, conducted in 75 centres in Europe, Israel and Canada, 1400 patients with refractory unstable angina and culprit coronary artery lesions suitable for angioplasty or atherectomy were randomised to c7E3 Fab or placebo. The drug was administered for 18 to 24 hours prior to the interventional procedure and continued through 1 hour after. Patients were followed for adverse events such as death, myocardial infarction and recurrent ischaemia requiring urgent intervention. Preliminary findings again demonstrated a significant reduction of 30-day composite events in patients treated with c7E3 Fab with efficacy far exceeding the predetermined stopping level 29 (10.8% composite event rate in c7E3 Fab-treated patients compared to 16.4% in placebo patients, $P = 0.0064$). Major bleeding rates were found to be acceptably low (2.9% in treated patients versus 1.7% in placebo).

Integrilin, a synthetic cyclic heptapeptide, was the next GP IIb/IIIa platelet antagonist to be evaluated as an adjunct to PTCA. Initial experience with this class of agents was obtained in IMPACT-I (Integrilin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis) and IMPACT High/Low dose ranging studies.^{29,30} IMPACT-II, a follow-up phase III study, randomised 4010 patients undergoing routine angioplasty to one of three arms of treatments: bolus integrilin (135 µg/kg) followed by 0.5 µg/kg/min infusion for 24 hours, bolus followed by 0.75 µg/kg/min infusion for 24 hours and placebo. All patients received heparin and aspirin prior to the procedures. The primary endpoint was the 30-day composite of death, myocardial infarction, need for urgent intervention and stenting for abrupt closure. integrilin was only modestly effective in preventing abrupt closure in patients undergoing coronary angioplasty and reducing ischaemic events at 30 days (unpublished data). The composite efficacy of low- and high-dose integrilin at 30 days was 9.1% ($P=0.035$) and

10.0% ($P = 0.178$) respectively compared to placebo of 11.6%. These benefits were achieved without any increased bleeding risk.

Finally, GP IIb/IIIa antagonists were also found to be beneficial in reducing ischaemic complications when used in percutaneous debulking interventional procedures. In IMPACT-II, integrilin markedly suppressed composite 30-day ischaemic endpoint (death, MI, urgent bypass, repeat angioplasty or stent) in patients who underwent rotational atherectomy.³¹ Benefits were also evident in patients undergoing directional atherectomy in EPIC, with a 70% reduction in the incidence of non-Q myocardial infarction. In addition, c7E3 Fab appears to be effective in reducing the rate of distal embolization and incidence of non-Q MI associated with saphenous vein graft intervention.³² This may have an important impact on the current practice of percutaneous intervention in diseased saphenous venous grafts. Trials defining the role of GP IIb/IIIa antagonists in coronary stenting are currently being conducted.

The initial successes from c7E3 and integrilin have spawned more trials of other GP IIb/IIIa antagonists to similarly prevent ischaemic complications in coronary angioplasty (Table II). The largest is the RESTORE (Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis) trial of tirofiban, a nonpeptide derivative of tyrosine. In this trial, 2100 patients were randomised equally to receiving tirofiban and placebo. There was a significant 38% reduction in the composite ischaemic endpoint of tirofiban-treated patients compared to placebo patients (8.7% versus 5.4%, $P = 0.005$) at 2 days (unpublished data). The benefit was, however, not evident at 30 days of follow-up.

The disappointing results of integrilin and tirofiban in reducing angioplasty-related ischaemic complications

TABLEII: GLYCOPROTEIN IIb/IIIa INHIBITORS: PHASE 3 CLINICAL TRIALS

Trial	Number	Drug	Status
Coronary interventions			
EPIC	2099	Abciximab	Completed
IMPACT-II	4010	Integrilin	Completed
EPILOG	2792	Abciximab	Completed
RESTORE	2100	Tirofiban	Completed
Unstable angina			
CAPTURE	1266	Abciximab	Completed
PURSUIT	10,400	Integrilin	In progress
PARAGON	~10,000	Lamifiban	In progress
PRISM	~3000	Tirofiban	In progress
Acute myocardial infarction			
IMPACT-AM1	150	Integrilin	Completed
PARADIGM II	~ 10,000	Lamifiban	In progress

TABLE III: DIFFERENCES BETWEEN NON COMPETITIVE AND COMPETITIVE GP IIb/IIIa INHIBITORS

	Non competitive inhibitors (Example: c7E3 Fab)	Competitive Inhibitors (Example: Integrilin™)
Binding to GP IIb/IIIa receptor	Irreversible	Reversible
Specificity for GP IIb/IIIa receptor	Cross-reactivity with other integrin receptors	High specificity, no cross-reactivity
Plasma half-life	Short	Short
Biological half-life	Long (~4 to 6 hours)	Short (~30 minutes to 2 hours)
Duration of antiplatelet effect	May persist for days after cessation of infusion	Dose-dependent, stops with cessation of infusion
Bleeding risk	High	Low
Immunogenicity risk	Significant	Absent

when compared to c7E3 Fab, have been attributed to several possible causes. These include fundamental differences in the pharmacologic and pharmacokinetic properties between the noncompetitive (for example, c7E3 Fab) and competitive GP IIb/IIIa inhibitors (for example, tirofiban) (Table III). The model noncompetitive inhibitor, c7E3 Fab, binds to a receptor more or less permanently and has a long biological half-life. Recovery of platelet aggregation occurs as a result of externalization of new GPIIb/IIIa receptors and release of fresh megakaryocytes from the bone marrow, and not from dissociation of the drug. This prolonged effect that extends beyond the duration of infusion may explain the clinical benefits seen with c7E3 Fab in the prevention of ischaemic complications in acute coronary syndromes compared with the short-acting competitive inhibitors. In addition, the ability of the c7E3 Fab to cross-react with other integrins such as vitronectin receptors may account for its sustained effect in reducing late clinical restenosis.

Role of GP IIb/IIIa Antagonists in Acute Coronary Syndromes: Acute Myocardial Infarction

Despite promising results in animal models, there have been few human studies of the combined use of thrombolytics and GP IIb/IIIa blockade in the setting of acute myocardial infarction. This is largely due to initial concern over the risk of possible catastrophic bleeding with combined potent anticoagulant, antiplatelet, and thrombolytic therapies. To date, only two small trials have been completed, TAMI-8 and IMPACT-AMI. In the TAMI 8 trial,³³ 60 patients with acute myocardial infarction were enrolled and given m7E3 Fab between 3 and 15 hours after tPA. Though limited by the small study population, there was evidence of improved arterial patency at 24 hours as well as a trend towards less recurrent ischaemia and no increase in bleeding risk. Another encouraging study utilized integrilin in conjunction with accelerated tPA in a similar setting.³⁴ Preliminary findings showed a trend towards improved patency of the infarct-related artery at 90 minutes. In addition, the study also showed that larger doses of integrilin are

required to bring about effective platelet inhibition, suggesting that platelets are markedly activated during acute myocardial infarction.

The latest GP IIb/IIIa antagonists to be evaluated in the setting of acute myocardial infarction is the non-peptide, lamifiban. In the PARADIGM study (Platelet Aggregation Receptor Antagonist Dose Investigation for Reperfusion Gain in Myocardial Infarction), patients are being randomised to lamifiban or placebo in conjunction with front-loaded tPA. The primary endpoint is the composite of reperfusion failure (based on 90-minute angiography), death, reinfarction, refractory ischaemia, need for non-elective revascularisation, or persistent or recurrent ST-segment elevation by continuous monitoring.³⁵

Role of GP IIb/IIIa Antagonists in Acute Coronary Syndromes: Unstable Angina Pectoris

The underlying pathophysiology of unstable angina pectoris is the rupture of an atherosclerotic plaque and its subsequent formation of nonocclusive thrombus. Pharmacologic treatment with aspirin and heparin can only partially alleviate the marked platelet activation and thrombin generation that occur. Small pilot studies of c7E3 Fab and integrilin have shown consistent benefits in reducing ischaemic outcomes in treated patients.³⁶⁻³⁸ These early encouraging findings have prompted three large phase III trials examining GP IIb/IIIa blockade in patients with unstable angina pectoris, including PURSUIT (using integrilin), PARAGON (using lamifiban) and PRISM (using tirofiban).

Complications of GP IIb/IIIa Blockade Treatment

The most common complication of GP IIb/IIIa antagonism, particularly with the use of c7E3 Fab, has been increased bleeding. In coronary intervention, it appears that weight-adjusted heparin (70 IU/kg bolus, to attain an activated clotting time of between 200 and 300 seconds) with aggressive vascular access site management, should address these concerns.

In EPIC trial, thrombocytopenia has been noted to occur more frequently in c7E3-treated patients than

placebo. Thrombocytopenia (defined as <100 000 platelets/ul) and severe thrombocytopenia (defined as <50 000 platelets/ul) occurred in 5.2% and 1.6% of bolus and infusion recipients compared to 3.4% and 0.7% of placebo recipients. Fortunately, this did not translate into increased haemorrhagic complications. In situations which require rapid reversal of the antiplatelet effect of c7E3 Fab, transfusion with a pack of random donor platelets is recommended. The potential advantages of the newer synthetic GPIIb/IIIa antagonists are that they do not appear to cause thrombocytopenia or other immunogenically mediated responses, and they are more readily reversible.

Human-anti chimeric antibody (HACA) may develop in response to c7E3 Fab. It is observed in 6.5% of c7E3 treated patients in the EPIC trial. To date, this has not been of clinical significance. More serious allergic and hypersensitivity reactions have yet to be reported.

Care of Patients Receiving GP IIb/IIIa Antagonists

Studies have established the association between heparin dosing regimen and the risk of bleeding in patients receiving c7E3 Fab. Besides using low-dose weight-adjusted heparin regime during interventions, certain basic practice guidelines and nursing care techniques should also be observed to reduce bleeding complications. These include careful attention to the technique of establishing vascular access, avoidance of insertion of venous sheaths and early removal of sheaths on the same day (within 4 to 6 hours after completion of procedure).³⁹ By adopting a standardized nursing approach to patients receiving c7E3 Fab,⁴⁰ successful outcomes will most times be achieved and safety profile be optimized.

Conclusions

The proven clinical efficacy of c7E3 Fab in preventing ischaemic complications during coronary intervention represents a significant medical triumph for the process of basic scientific inquiry leading to clinical investigation. The role of GP IIb/IIIa antagonists in acute coronary syndromes is similarly encouraging, although large-scale randomised trial results are needed before its routine use can be recommended. There are many questions that still need to be answered concerning the use of this group of antiplatelet agents. These include optimal dosing and treatment duration, interactions with thrombolytics and antithrombotics, long-term safety and effectiveness and use with coronary stents. Further research into the molecular biology of plaque formation and restenosis will undoubtedly contribute to an expanded application of this therapy in the other thromboembolic disorders.

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