Platelet glycoprotein IIb/IIIa receptor antagonists in coronary artery disease

Introduction

Contemporary approaches to the treatment of coronary artery thrombosis focus on control of thrombin formation and activity, lysis of already-formed clot and inhibition of platelet aggregation. Each of these strategies has continued to evolve as our understanding of the processes of atherosclerosis and thrombosis improves and newer, novel and potentially more effective agents are developed. In particular, the role of platelet inhibition has received a great deal of attention recently. While the most widely used agent, aspirin, is clearly safe and effective, it is well-known that its anti-platelet effects are relatively weak. Drugs that block the platelet glycoprotein IIb/IIIa receptor — a membrane receptor that binds fibrinogen and mediates the final common pathway to platelet aggregation — have recently become available for clinical use. These agents have the potential to become a crucial strategy for therapeutic control of platelet function and are currently undergoing extensive evaluation in the settings of percutaneous coronary intervention and acute coronary syndromes. This article will review the current role of antiplatelet therapy in thrombotic cardiovascular disease and provide an in-depth report of the current clinical status of the new class of drugs known as glycoprotein IIb/IIIa receptor antagonists.

Aspirin: do we need a better antiplatelet agent?

The abundance of evidence demonstrating the central role of platelets in acute coronary syndromes underscores the critical need for effective anti-platelet therapy. Plaque fissuring or rupture exposes subendothelial components and the lipid-rich core which are highly thrombogenic. Marked platelet and coagulation system activation result, leading to the dynamic formation of occlusive intracoronary thrombus responsible for the clinical syndromes. The incorporation of platelets into the forming thrombus can also delay or diminish the success of pharmacological thrombolysis, as platelet-rich thrombi are more resistant to lysis than erythrocyte-rich thrombi. Furthermore, thrombolytic therapy itself can trigger platelet activation, while the thrombin generation associated with thrombolysis is also a potent stimulator of platelets. Likewise, coronary angioplasty is associated with plaque fracture and splitting and medial disruption. Platelet deposition and mural thrombus formation occur to varying degrees and platelet activation during angioplasty has been well-described in animal models and in humans. In turn, platelet thrombus formation has been implicated in abrupt vessel closure during and immediately after angioplasty, and in the process of restenosis.

Having established the need for effective antiplatelet therapy in thrombotic cardiovascular disease, it is hard to argue against the remarkable success of aspirin. It has proven to be of benefit in hundreds of clinical trials, and is now used routinely in patients with myocardial infarction, unstable angina, and in those undergoing coronary angioplasty. Aspirin acts by inactivating prostaglandin G/H synthase via selective acetylation of the enzyme. This produces a permanent loss of the enzyme's cyclo-oxygenase activity, the first step in the conversion of arachidonic acid to thromboxane A2. However, thromboxane A2 is just one of over 90 agonists that can stimulate platelet aggregation. Accordingly, blockade of its formation will not prevent platelet aggregation by other agonists such as thrombin, the most potent agonist of platelet aggregation known. On the other hand, inhibition of the platelet glycoprotein IIb/IIIa receptor, the final common pathway to platelet aggregation, prevents platelet aggregation irrespective of the agonist. The development of agents that block the GP IIb/IIIa receptor thus offers a logical and strategic method of achieving greater control of platelet function.

The glycoprotein IIb/IIIa receptor in platelet function

The interrelated processes of platelet adhesion, platelet activation and platelet aggregation follow vessel injury, leading to the formation of the initial haemostatic platelet plug. While adhesion of platelets to the damaged vessel site is dependent on the recognition of adhesive proteins by several platelet membrane glycoproteins, the GP IIb/IIIa receptor is the principal receptor involved in platelet aggregation. Platelet activation triggers conformational changes in the unactivated GP IIb/IIIa receptor that transform it into its activated,
ligand-competent state. This receptor then binds mainly fibrinogen which is the key event in the process of platelet aggregation. The fibrinogen molecules form cross-bridges between adjacent platelets, linking them together to form a scaffold for the advancing haemostatic plug.

The GP IIb/IIIa receptor (a1b2/3) belongs to the integrin family of heterodimeric adhesion molecules, which are formed by the non-covalent interaction of a series of a and b subunits[26]. Integrins are found on virtually all cell types and mediate a diversity of physiological responses. Several other integrins are present on the platelet surface in addition to GP IIb/IIIa, many of which are involved in platelet adhesion. Figure 1 illustrates the structure of GP IIb/IIIa — a typical example of an integrin. The GP IIb/IIIa receptor is the most abundant on the platelet surface, with approximately 50 000 copies per platelet. Apart from its ability to bind fibrinogen, the receptor can bind other adhesive proteins such as fibronectin, vitronectin and von Willebrand factor[27–29]. However, these proteins appear to have only minor roles in the process of aggregation[27].

Two specific peptide sequences present in adhesive proteins are involved in binding to the GP IIb/IIIa receptor. The Arg-Gly-Asp (RGD) sequence was initially identified as the adhesive sequence in fibronectin[30], but is also present in fibrinogen, von Willebrand factor and vitronectin. All these proteins contain at least one RGD sequence, while fibrinogen contains two RGD sequences per half molecule[31]. The other major sequence involved is the Lys-Gln-Ala-Gly-Asp-Val (KQAGDV) sequence, located at the extreme carboxy terminus of the y-chain of fibrinogen[32,33]. Unlike the RGD sequence, this sequence is only found in fibrinogen. Electron microscopic and immunological studies strongly suggest that the y-chain sequence is the predominant site for fibrinogen-GP IIb/IIIa binding[34,35], although the relationship between this sequence and the RGD binding sites is still not fully understood. A 'multiple contact' model has been suggested in which RGD and y-chain containing peptides have preferred, but also shared contact sites, and these multiple contacts contribute to the overall high-affinity binding of fibrinogen to the GP IIb/IIIa receptor[31].

Monoclonal antibodies were the first agents developed with specific activity against the GP IIb/IIIa receptor. Collier and colleagues[36] were responsible for the development of 7E3, a murine antibody which has subsequently undergone considerable refinement. The Fc fragment of the antibody was cleaved to avoid immunogenicity and a chimeric compound was formed by combining the murine Fab fragments with the constant regions of human immunoglobulin to form chimeric 7E3 Fab (c7E3) (Fig. 2). This compound has been renamed abciximab, and has already undergone extensive clinical evaluation, particularly in the setting of high risk coronary angioplasty. While other monoclonal antibodies directed against GP IIb/IIIa have also been developed[37,38], these have not progressed to clinical testing.

All other GP IIb/IIIa antagonists currently undergoing clinical evaluation are based on the RGD template. The early synthetic linear peptide compounds, based on the RGD sequence, were found to be unstable and relatively ineffective. Cyclization of the protein provided greater protection from enzymatic breakdown and improved potency[39,40]. The cyclic peptide, Integrelin (COR Therapeutics, South San Francisco, CA), utilizes a KGD rather than RGD sequence (lysine substituted for arginine) as the basis of its design. Peptide derivatives including Tirofiban (Merck West Point, PA) and Lamifiban (Hoffman La-Roche, Basel, Switzerland) were developed to overcome some of the problems of peptide compounds such as instability and short survival time. Agents that can be administered orally have also been developed and are designed either as pro-drugs, which are metabolized to the active form after ingestion, or as inherently orally active agents[40]. Table 1 provides a listing and classification of several GP IIb/IIIa antagonists that have recently been evaluated in clinical trials.
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Table 1 A classification and examples of GP IIb/IIIa receptor antagonists recently developed

| Monoclonal antibodies         | Abciximab (previously known as chimeric 7E3 Fab) |
| Cyclic RGD peptides          | MK-852                                      |
|                              | DMP-728                                     |
|                              | TP-9201                                     |
|                              | SC-54701                                    |
|                              | G4120                                       |
| KGD peptides                 | Integrelin                                  |
| Peptide derivatives          | Lamifiban (previously known as Ro 44-9883)  |
|                              | Tirofiban (previously known as MK-383)       |
| Orally active agents         | Xemifiban (previously known as SC-54684)    |
|                              | Fradafliban (previously known as BIBU-104)  |
|                              | GR144053                                    |

**Clinical studies with glycoprotein IIb/IIIa receptor antagonists (Table 2)**

**Coronary angioplasty**

Early studies with abciximab helped establish the potential benefit of GP IIb/IIIa receptor inhibition during coronary angioplasty\[41\] and provided vital information regarding the relationship between appropriate dosing and degree of receptor blockade\[42\] (Tcheng, 1994 No. 108). The first large-scale trial to evaluate GP IIb/IIIa receptor inhibition in coronary intervention was the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial\[43,44\]. This trial enrolled 2099 patients at higher than normal risk for coronary intervention. Patients were randomly assigned to receive a bolus of c7E3, a bolus plus a 12 h infusion of c7E3 or placebo. All patients received aspirin prior to the procedure and heparin was administered during the procedure and continued for a further 12–24 h.

The principal finding of this trial was a marked reduction in ischaemic events with c7E3 treatment. A clear dose response was observed in the reduction in the 30-day composite endpoint, comprising death, non-fatal myocardial infarction, urgent repeat PTCA or coronary artery bypass surgery, stent insertion for abrupt closure or intraaortic balloon counterpulsation for recurrent ischaemia (Fig. 3). A bolus and 12 h infusion of c7E3 resulted in a 35% reduction in the composite event rate from 12-8% in patients who received placebo to 8-3% in the bolus and infusion c7E3 group. While there were no differences in death rates among the three study arms, two patients in the bolus plus infusion group died

Table 2 Recently completed trials of glycoprotein IIb/IIIa receptor antagonists in ischaemic heart disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>No of patients</th>
<th>GP IIb/IIIa receptor antagonist</th>
<th>Clinical setting</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellis et al.[42]</td>
<td>1993</td>
<td>27</td>
<td>m7E3</td>
<td>PTCA</td>
<td>Dose-ranging</td>
</tr>
<tr>
<td>Tcheng et al.[79]</td>
<td>1994</td>
<td>56</td>
<td>c7E3</td>
<td>PTCA</td>
<td>Dose-ranging placebo-controlled</td>
</tr>
<tr>
<td>IMPACT-I[90]</td>
<td>1994</td>
<td>150</td>
<td>Integrelin</td>
<td>PTCA</td>
<td>Randomized placebo-controlled</td>
</tr>
<tr>
<td>Harrington et al.[81]</td>
<td>1994</td>
<td>73</td>
<td>Integrelin</td>
<td>PTCA</td>
<td>Dose-ranging placebo-controlled</td>
</tr>
<tr>
<td>Keriakes et al.[81]</td>
<td>1994</td>
<td>86</td>
<td>Tirofiban</td>
<td>PTCA</td>
<td>Randomized placebo-controlled</td>
</tr>
<tr>
<td>EPIC[93,94]</td>
<td>1994</td>
<td>2099</td>
<td>c7E3</td>
<td>PTCA</td>
<td>Randomized placebo-controlled</td>
</tr>
<tr>
<td>Lincoff et al.[76]</td>
<td>1995</td>
<td>103</td>
<td>Integrelin</td>
<td>PTCA</td>
<td>Randomized placebo-controlled</td>
</tr>
<tr>
<td>IMPACT II[95]</td>
<td>1995</td>
<td>4010</td>
<td>c7E3</td>
<td>UAP</td>
<td>Randomized placebo-controlled</td>
</tr>
<tr>
<td>Simoons et al.[96]</td>
<td>1994</td>
<td>60</td>
<td>Integrelin</td>
<td>UAP</td>
<td>Randomized placebo-controlled</td>
</tr>
<tr>
<td>Schulman et al.[93]</td>
<td>1993</td>
<td>227</td>
<td>Lamifiban</td>
<td>UAP</td>
<td>Randomized placebo-controlled</td>
</tr>
<tr>
<td>Theroux et al.[52]</td>
<td>1994</td>
<td>360</td>
<td>Lamifiban</td>
<td>UAP</td>
<td>Randomized placebo-controlled</td>
</tr>
<tr>
<td>Theroux et al.[53]</td>
<td>1994</td>
<td>103</td>
<td>Tirofiban</td>
<td>UAP</td>
<td>Randomized placebo-controlled</td>
</tr>
<tr>
<td>TAMI-L[54]</td>
<td>1993</td>
<td>70</td>
<td>m7E3</td>
<td>AMI</td>
<td>Dose-ranging placebo-controlled</td>
</tr>
<tr>
<td>Ohman et al.[55]</td>
<td>1994</td>
<td>85</td>
<td>Integrelin</td>
<td>AMI</td>
<td>Dose-ranging placebo-controlled</td>
</tr>
</tbody>
</table>

c7E3 = chimeric 7E3 Fab; PTCA = percutaneous transluminal coronary angioplasty; AMI = acute myocardial infarction; UAP = unstable angina.
without ever receiving the drug. Both the rate of non-fatal myocardial infarction and the incidence of urgent revascularization procedures were significantly reduced. Notably, the greatest effect of c7E3 was in the reduction of myocardial infarction rather than the need for repeat emergency intervention.45

A number of patients subgroups appeared to gain particular benefit from GP IIb/IIIa receptor blockade. Patients with unstable angina who received bolus and infusion of c7E3 had significant reductions in the incidence of death and non-fatal myocardial infarction and tended to have less repeat interventions, which overall, added up to a 70% reduction in the composite endpoint event rate.46 Similarly, patients undergoing angioplasty for acute myocardial infarction derived significant benefit from c7E3 bolus and infusion, while patients who underwent directional atherectomy and received c7E3 had lower rates of non Q-wave myocardial infarction than directional atherectomy patients who received placebo.47

The EPIC trial also demonstrated a significant reduction in recurrent ischaemic events up to 6 months with c7E3 treatment. Using a composite of death, myocardial infarction, elective bypass surgery or elective angioplasty, c7E3 bolus and infusion reduced the composite event rate from 35% in the placebo group to 27% in the bolus plus infusion group—a 26% reduction in ischaemic events. In contrast, bolus of c7E3 alone had little effect.48 The benefit on clinical restenosis was largely due to a lower incidence of repeat revascularization in patients with initially successfully procedures, with repeat target vessel revascularization rates reduced from 22% in the placebo group to 16% in the c7E3 bolus plus infusion group. As a result, this study was the first large-scale randomized trial to show a clinically meaningful reduction in long-term ischaemic outcomes following coronary intervention.

The major drawback of c7E3 treatment to emerge from the EPIC trial was the increased risk of bleeding (Table 3). There was a twofold increase in major bleeding episodes and transfusion rates in c7E3 treated patients. Most bleeding events were related to femoral artery puncture sites or subsequent coronary artery bypass surgery. Particular patient groups were at higher risk for bleeding events including females, patients with low body weight, those who underwent prolonged procedures and patients undergoing PTCA for acute myocardial infarction.

The KGD peptide Integrelin has also undergone extensive evaluation in the setting of coronary angioplasty. The pilot Integrelin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis

### Table 3 Major bleeding and transfusion rates in recently completed trials of GP IIb/IIIa receptor antagonists

<table>
<thead>
<tr>
<th>Reference</th>
<th>GP IIb/IIIa antagonist</th>
<th>Dosing regimen</th>
<th>Major bleeding (%)</th>
<th>Transfusions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellis et al.42</td>
<td>m7E3</td>
<td>0-15-0.35 mg. kg⁻¹ bolus (n=23)</td>
<td>4-3</td>
<td>4-3</td>
</tr>
<tr>
<td>Tcheng et al.79</td>
<td>c7E3</td>
<td>0-15-0.25 mg. kg⁻¹ bolus (n=5)</td>
<td>6-4</td>
<td>2-1</td>
</tr>
<tr>
<td>Simoons et al.54</td>
<td>c7E3</td>
<td>0-25 mg. kg⁻¹ bolus+10 μg. min⁻¹ infusion (n=32)</td>
<td>3-3</td>
<td>10-0</td>
</tr>
<tr>
<td>EPIC Trial43,44</td>
<td>c7E3</td>
<td>0-25 mg. kg⁻¹ bolus+10 μg. min⁻¹ infusion (n=30)</td>
<td>12-5</td>
<td>14-3</td>
</tr>
<tr>
<td>Harrington et al.80</td>
<td>Integrelin</td>
<td>90-180 μg. kg⁻¹ bolus+0-5-1.0 μg. kg⁻¹.min⁻¹ infusion (n=54)</td>
<td>3-7</td>
<td>3-7</td>
</tr>
<tr>
<td>Schulman et al.73</td>
<td>Integrelin</td>
<td>90-180 μg. kg⁻¹ bolus+10 μg. kg⁻¹.min⁻¹ infusion (n=76)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IMPACT61</td>
<td>Integrelin</td>
<td>90 μg. kg⁻¹ bolus+10 μg. kg⁻¹.min⁻¹ infusion (n=103)</td>
<td>4-9</td>
<td>7-8</td>
</tr>
<tr>
<td>IMPACT61</td>
<td>Lamifiban</td>
<td>1-0-5 μg. min⁻¹ bolus (n=239)</td>
<td>2-9</td>
<td>N/A</td>
</tr>
<tr>
<td>Theroux et al.13</td>
<td>m7E3</td>
<td>0-10-0.25 mg. kg⁻¹ bolus (n=60)</td>
<td>25-0</td>
<td>20-0</td>
</tr>
<tr>
<td>Lincoff et al.78</td>
<td>c7E3</td>
<td>0-25 mg. kg⁻¹ bolus+10 μg. min⁻¹ infusion + heparin 100 U. kg⁻¹ bolus (n=51)</td>
<td>1-9</td>
<td>4-8</td>
</tr>
<tr>
<td>Theroux et al.13</td>
<td>c7E3</td>
<td>0-25 mg. kg⁻¹ bolus+10 μg. min⁻¹ infusion + heparin 70 U. kg⁻¹ bolus (n=52)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RBCs = red blood cells; N/A = data not available

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Figure 4  Graphs comparing the primary 30-day efficacy endpoint, the incidence of death or myocardial infarction, and the need for repeat urgent intervention among the three study arms in the IMPACT II trial. ■ = placebo (n = 1328); □ = low dose Integrelin (n = 1349); △ = high dose Integrelin (n = 1333).

(IMPACT-I) trial was a dose-ranging study in 150 patients undergoing routine coronary intervention. This trial demonstrated a reduction in ischaemic events and no excess of bleeding with a 12 h infusion of Integrelin. These encouraging results led to the much larger IMPACT-II trial whose results were recently presented at the European Congress in Amsterdam. This trial enrolled 4010 patients undergoing coronary intervention. Patients were randomly assigned to receive a bolus of 135 μg . kg⁻¹ and 24-h low-dose infusion (0.5 μg . kg⁻¹ . min⁻¹) of Integrelin, a bolus and high-dose (0.75 μg . kg⁻¹ . min⁻¹) infusion or placebo. Aspirin and heparin were also administered.

This trial demonstrated only a trend in reduction of ischaemic events among Integrelin-treated patients compared with placebo. The primary, 30-day, composite efficacy endpoint comprising death, non-fatal myocardial infarction, emergency re-intervention, emergency coronary artery bypass surgery or stent placement for abrupt closure, was 11.4% with placebo, 9.2% with low-dose Integrelin and 9.9% with high-dose Integrelin. This represented a 19% reduction for low-dose Integrelin (P = 0.06) and a 13% reduction for high dose (P = 0.22). The more favourable response with low-dose rather than high-dose Integrelin, in terms of the composite endpoint, the incidence of death or myocardial infarction and the need for repeat urgent intervention was unexpected (Fig. 4). However, the bolus was the same for both Integrelin dose arms and most of the events occurred quite early, particularly within 6 h. This is at a timepoint when the difference in infusion levels may not have contributed to clinical outcomes. Secondary analysis of individual endpoints demonstrated that Integrelin significantly reduced the incidence of emergency stent placements, and low-dose Integrelin in particular, reduced the occurrence of death or Q wave myocardial infarction. Also, the analysis of actually treated patients rather than by Intention-to-treat, was statistically significant in favour of Integrelin. Despite evidence of borderline benefit, it is noteworthy that both low- and high-dose Integrelin treatments significantly decreased ischaemic events during the first 24 h — the period in which the infusions were administered. In the early phase, there was a 31% reduction in events from 9.6% to 6.9% (P = 0.006) with low dose Integrelin treatment.

The IMPACT II trial comprised a number of patient subgroups including 380 patients who underwent rotational atherectomy. Of some concern was that ischaemic events occurred in 19.9% of the placebo group, almost twice the rate of 10.4% observed in placebo patients who did not undergo rotational atherectomy. This excess of ischaemic events was mainly reflected in the 14.5% incidence of post-procedural myocardial infarction and a 7.6% incidence of emergency bypass surgery in patients undergoing rotational atherectomy. Integrelin treatment reduced the composite endpoint rate to 12.4% (P = 0.11), lowering myocardial infarction rates by 26% and the rate of emergency CABG to 2.1%. In contrast to rotational atherectomy, Integrelin treatment did not tend to improve outcomes in the 522 patients who underwent directional atherectomy.

The IMPACT II trial also included a 6 month angiographic follow-up substudy to assess the effect of Integrelin on restenosis. Eight hundred and eighteen patients were enrolled in the substudy, of which 617 (78%) had follow-up data available for analysis. A disappointing trend was observed for increased restenosis rates with Integrelin use. Using an average of two angiographic views, 47% of patients in the placebo group had a diameter stenosis greater than 50% compared with 48% in the low-dose Integrelin group and 56% in the high-dose Integrelin group. The average net gain in luminal diameter was actually greater in the placebo group (0.43 mm placebo vs 0.38 mm Integrelin, P = 0.052), with the least effect noted in the high-dose Integrelin group.

Unstable angina

A number of phase II clinical trials have now been completed evaluating GP IIb/IIIa receptor inhibition in unstable angina. In the largest of these trials to date, 360 patients with chest pain within the previous 24 h were randomized to placebo, or one of four escalating doses of Lamifiban. All patients received aspirin, but heparin was administered at the discretion of the treating physician. Lamifiban appeared clinically beneficial with a significant reduction in death, myocardial infarction or need for urgent intervention demonstrated during the infusion period (up to 5 days) from 8.2% in the control group to 3.4% in all Lamifiban groups. At 1-month follow-up, there was also a significant decrease in the incidence of death and myocardial infarction in the high-dose Lamifiban groups. The incidence of major bleeding complications was 2.9% in Lamifiban treated patients, and was not statistically different from the placebo group bleeding rate of 0.8%. Interestingly, the addition of heparin did not seem to add to the efficacy of Lamifiban, but did increase the bleeding risk. These results provided the background for the phase III Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON) trial which its currently evaluating Lamifiban in the setting of unstable angina and non-Q wave myocardial infarction.
Several other GP IIb/IIIa receptor antagonists have been evaluated in unstable angina in smaller phase II trials (Table 2). In a multicentre trial involving 17 centres, 89 patients were randomized to either low dose Integrelin (45 μg. kg⁻¹ bolus plus 0·5 μg. kg⁻¹ min⁻¹ infusion), high dose Integrelin (90 μg. kg⁻¹ bolus plus 1·0 μg. kg⁻¹ min⁻¹ infusion) or placebo. All patients received intravenous heparin, and the placebo group also received aspirin. After 24 h infusion, high dose Integrelin was found to decrease both the number and duration of ischaemic events detected by continuous ST-segment monitoring, without an excess in bleeding episodes[53]. Positive results were also obtained in a pilot study of c7E3 in patients with refractory unstable angina[54]. In this multicentre trial, 60 patients with angina at rest unresponsive to maximal drug therapy, and who had electrocardiographic changes, were randomized to receive a 24 h infusion of c7E3, or heparin. Patients receiving c7E3 had less recurrent ischaemia, fewer myocardial infarctions, and less need for urgent angioplasty or bypass surgery. The incidence of ischaemic events was reduced from 20% in the placebo group to 3% in the c7E3 group. A pilot study with the non-peptide, Tirofiban in 71 patients with unstable angina demonstrated a trend towards a reduction in the incidence of refractory angina[55]. The consistently beneficial and encouraging results of these pilot trials has led to a number of large-scale phase III clinical trials with these agents in unstable angina which are currently ongoing.

Acute myocardial infarction

Compared with the clinical situations of coronary angioplasty and unstable angina, there have been relatively few clinical trials to date of GP IIb/IIIa receptor inhibitor use in acute myocardial infarction. This is despite a great deal of experimental and animal work that support the benefit of potent platelet antagonism as an adjunct to thrombolysis[56-59]. The Eighth Thrombolysis and Myocardial Infarction (TAMI-8) project[60] evaluated murine 7E3 Fab (m7E3) use following tissue plasminogen activator (t-PA) thrombolysis, given in an escalating dose regimen at variable times (3, 6 and 15 h) after t-PA. There was evidence of improved vessel patency at 24 h, and a trend towards less recurrent ischaemia in the m7E3 groups. The study also demonstrated a consistent, dose-dependent inhibition of platelet aggregation. Bleeding episodes were not increased. Although not specifically designed as a trial in myocardial infarction, the EPIC trial included 64 patients who underwent PTCA for acute myocardial infarction — 42 had direct PTCA and 22 had rescue PTCA for failed reperfusion after thrombolytic therapy. Even in this small subgroup, there was a significant reduction in adverse clinical changes, were randomized to receive a 24 h infusion of c7E3, or heparin. Patients receiving c7E3 had less recurrent ischaemia, fewer myocardial infarctions, and less need for urgent angioplasty or bypass surgery. The incidence of ischaemic events was reduced from 20% in the placebo group to 3% in the c7E3 group. A pilot study with the non-peptide, Tirofiban in 71 patients with unstable angina demonstrated a trend towards a reduction in the incidence of refractory angina[55]. The consistently beneficial and encouraging results of these pilot trials has led to a number of large-scale phase III clinical trials with these agents in unstable angina which are currently ongoing.

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The Integrelin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis — Acute Myocardial Infarction (IMPACT-AMI) trial is the largest trial to date of thrombolysis and conjunctive GP IIb/IIIa receptor inhibition. In the first phase of this trial, Integrelin was administered with accelerated t-PA, heparin and aspirin, to 132 patients in an escalating dose regimen. Preliminary results have shown that profound inhibition of platelet aggregation could be achieved, although high levels of Integrelin were required. There was a trend towards greater restoration of normal (Thrombolysis in Myocardial Infarction [TIMI] grade III) flow with Integrelin therapy, assessed at 90 min after commencement of treatment[69]. Currently Lamifiban is being evaluated in conjunction with streptokinase and t-PA in an international trial known as Platelet Aggregation Receptor Antagonist Dose Investigation for Reperfusion Gain in Myocardial Infarction (PARADIGM).

Unresolved issues

Comparative efficacy of the various GP IIb/IIIa antagonists

To date, there are no direct head-to-head comparisons of the various agents currently available. However, the results of the EPIC and IMPACT II trials raise the important question of whether the differences in the two trials’ findings is related to differences in the pharmacological profiles of the agents. Abciximab differs from Integrelin in a number of respects. It is a relatively large molecular weight compound, with a much greater affinity for the GP IIb/IIIa receptor than Integrelin. Most of the injected bolus binds avidly to the receptor, with only a small additional amount necessary as an infusion to maintain adequate receptor blockade. This strong affinity is also responsible for a gradual return to normal platelet function following cessation of the infusion. In contrast, Integrelin has a short half-life and relatively little of the initial bolus of Integrelin becomes platelet bound. Thus, most of its effective dose is delivered as an infusion. As a result of Integrelin’s short half-life and lower affinity for the receptor, the end of infusion is associated with a more abrupt return to normal platelet function. These, and other factors, such as a greater variability in Integrelin’s metabolism, have been suggested as explanations for the lack of efficacy observed in the IMPACT II trial. Furthermore, because direct measurement of GP IIb/IIIa receptor blockade is not possible with Integrelin, some uncertainty exists regarding the appropriate dose required to achieve a target level of GP IIb/IIIa receptor blockade. The doses of Integrelin used in the pilot IMPACT I trial[50] were substantially different from those used in IMPACT II.
As mentioned above, the EPIC trial demonstrated that c7E3 use was associated with an excess bleeding risk. However, the EPIC trial also found a relationship between activated clotting time and risk of bleeding, indicating that weight adjustment of conjunctive heparin therapy may help reduce bleeding episodes. The strategy of heparin dose reduction with concomitant c7E3 administration was tested in the pilot PROLOG trial[76] in which 103 patients treated with c7E3 during PTCA were randomized to either standard weight-adjusted dose heparin or lower weight-adjusted dosing. Patients were also randomly assigned to early arterial sheath removal (within 6 h) or conventional timing (12-18 h). Lower dosing of heparin did not result in reduced efficacy or an increase in ischaemic complications. However, there was significant reduction in major bleeding events and need for blood transfusions with lower dose heparin and early sheath removal. Weight adjustment and lowering of heparin dose when c7E3 is administered concurrently is being evaluated in the large-scale Evaluation of PTCA to Improve Long-Term Outcome by c7E3 Glycoprotein Receptor Blockade (EPILOG) trial.

In contrast to the EPIC trial, bleeding did not emerge as a major problem with Integrelin in the dosage regimen chosen for the large-scale IMPACT II trial (REF). Major bleeding episodes were relatively uncommon, occurring in 4.8% of patients receiving placebo and 5.2% of patients receiving Integrelin. However, minor bleeding events did occur more frequently with Integrelin (13.0% vs 9.6% P=0.002). As in the EPIC trial, most bleeding events were related to vascular access sites, while retroperitoneal haemorrhage was rare. There were five haemorrhagic strokes in the entire patient cohort, two of which occurred in patients receiving placebo, suggesting no apparent excess risk of intracerebral bleeding in Integrelin use.

The incidence of bleeding with Lamifiban in a phase II trial in patients with unstable angina was also relatively low. However, as was found in the EPIC trial, the addition of intravenous heparin markedly increased the risk of bleeding. It remains uncertain how the various GP Ib/IIa receptor antagonists will compare with respect to their relative bleeding risks. Once again, differences in pharmacological profiles may be reflected in differences in bleeding risk. Nevertheless, bleeding remains a significant limitation to GP Ib/IIa receptor inhibitor use and continued attention needs to be directed at minimizing this risk during the ongoing evaluation of these agents.

The future

Despite the extensive testing of GP Ib/IIa receptor antagonists already conducted, many issues still need to be addressed. The application of potent platelet inhibition during coronary interventions with newer devices such as rotational atherectomy and stent insertion is an exciting but as yet, unproved strategy. Similarly, the place of GP Ib/IIa receptor inhibition in peripheral arterial and venous thrombosis, pulmonary embolism and thrombotic cerebrovascular disease remains to be determined. Refinements in the administration of these drugs and head-to-head comparisons of the various compounds also await further study. New compounds continue to be developed, including novel drugs not based on the RGD recognition sequence[77,78]. A number of large-scale trials with sample sizes ranging from 1200 to 12000 patients are currently underway to evaluate abciximab, Integrelin, Tirofiban and Lamifiban in coronary angioplasty, unstable angina and acute myocardial infarction. The results of these and other trials are eagerly awaited, as they will help establish the place and appropriate use of these powerful agents—the first generation of 'anti-integrins' to be used in the clinical arena of ischaemic heart disease.

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References


Prostacyclin in primary pulmonary hypertension

Introduction

Primary pulmonary hypertension is a disease of unknown etiology that affects predominantly young people and is marked by a natural course almost uniformly fatal. Primary pulmonary hypertension most commonly occurs in women and the median survival in most series ranges from 2-5 to 30 years from diagnosis, although patients with less severe disease can live longer. However, patients with evidence of severe heart failure have a substantially shorter life expectancy. The sustained increases of pulmonary artery pressure and pulmonary vascular resistance result initially in right ventricular hypertrophy and dilatation and subsequently in right heart dysfunction and failure. The only definitive therapy for the more advanced cases of primary pulmonary hypertension is heart-lung or lung transplantation; however, only a minority of suitable patients may be transplanted due to the limited number of centres with expertise to perform this procedure and the limited availability of donor organs. Moreover, in most series 4-year survival after surgery remains <50%. For these reasons all efforts should be made to enhance the medical treatment of this syndrome in order to stabilize the clinical condition of the patients and to reduce or delay the need for organ transplantation.

Pathogenetic and pathophysiologic considerations

Primary pulmonary hypertension is characterized pathologically by extensive remodelling of the pulmonary vasculature, with thrombotic depositions and proliferative changes such as intimal fibrosis, medial hypertrophy (Fig. 1), and plexiform lesions. The hypertrophy of the smooth muscle in the media together with the reduction of pulmonary vascular resistance obtained by vasodilator drugs led Paul Wood many years ago to describe the ‘vasoconstrictive’ hypothesis as the basis for understanding the pathogenesis and pathophysiology of primary pulmonary hypertension. He suggested that a component of active vasoconstriction of small muscular pulmonary arteries and arterioles was the main determinant of the haemodynamics and subsequent evolution of primary pulmonary hypertension. This concept induced many investigators to test a variety of vasodilator agents in patients with primary pulmonary hypertension in order to obtain a reduction of pulmonary artery resistance and of pulmonary artery pressure and an increase of cardiac index without symptomatic systemic hypotension. Methodological and pathophysiological considerations suggest that a convincing effect of pulmonary vasodilatation is achieved only in patients (responders) in whom a reduction of pulmonary artery pressure ≥15–20% is obtained in addition to a reduction of calculated pulmonary artery resistance of similar or greater extent. Many acute and long-term trials have shown that these goals may be achieved in approximately one fourth of patients, and only recently a trial using high doses of calcium channel antagonists (nifedipine up to 240 mg.·day⁻¹, diltiazem up to 720 mg.·day⁻¹) has shown an improvement in quality of life, regression of right ventricular hypertrophy and improved survival in the subgroup of acute responders. On the other hand, the overall beneficial effect on survival cannot be attributed solely to the vasodilator therapy as the acute responders could

[76] Lincoff AM, Tcheng JE, Bass TA et al. for the PROLOG Investigators. A multicenter, randomized, double-blind pilot trial of standard versus low dose weight-adjusted heparin in patients treated with platelet GPIIb/IIIa receptor antibody 7E3 during percutaneous coronary revascularization (abstr). J Am Coll Cardiol 1995; Special Issue: 80A