Newer Antiplatelets

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INTRODUCTION

Many therapeutic drugs have been identified that possess clinically important antiplatelet activity. Platelet inhibition can be achieved in numerous ways (Fig. 1), including inhibition of platelet cyclooxygenase, inhibition of ADP receptors or inhibition of the platelet glycoprotein (GP) IIb/IIIa receptor. Pharmacological inhibition of platelet function can also be achieved by interference with the function of the platelet glycoprotein IIb-IX receptor, synthetic peptides to the A1 Von Willebrand’s factor domain, recombinant Von Willebrand’s fragments covering the A1 domain, inhibition of the thromboxane synthase, blockade of endoperoxide-thromboxane receptors, modulation of platelet adeny or guanyl cyclase and peptides that bind to but do not activate the platelet-receptor domain that interacts with thrombin. This section focuses on new antiplatelet agents or new data with existing drugs which has clinical implications.

Prazugrel

Prazugrel (CS-747; LY-640315), a novel third-generation oral thienopyridine, a specific, irreversible antagonist of the platelet adenosine diphosphate ADP P2Y12 receptor. Recent studies showed prasugrel to be more efficacious in preventing ischemic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention; however, this is achieved at the expense of an increased risk of bleeding. Prasugrel provides more rapid and consistent platelet inhibition than clopidogrel1.

The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON) and Thrombolysis in Myocardial Infarction (TIMI) 38 demonstrated a further reduction in cardiovascular (CV) events among patients with moderate to high risk ACS who underwent percutaneous coronary intervention (PCI) and who were treated with prasugrel compared with clopidogrel2. The combination of aspirin and prasugrel led to a significant 19% relative reduction in the primary composite outcome of CV death, nonfatal myocardial infarction (MI) and nonfatal stroke compared with aspirin and clopidogrel among patients who underwent PCI with stent implantation for ACS. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, addition of clopidogrel to aspirin monotherapy was associated with a significant 20% relative risk reduction in the composite of CV death, nonfatal MI, and stroke.

Cilostazol

Cilostazol is a quinolinone derivative that inhibits cellular phosphodiesterase (more specific for phosphodiesterase III). The molecular formula of cilostazol is C20H27N5O2, and its molecular weight is 369.47. Cilostazol is 6-{4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy}-3,4-dihydro-2(1H)-quinolinone, CAS-73963-72-1.

The structural formula is:

![Structural formula of Cilostazol](image)
Cilostazol is indicated for the reduction of symptoms of intermittent claudication. It is also used off label for the prevention of restenosis following angioplasty either alone or in combination with other platelet inhibitors like aspirin and ticlopidine. Based on literature reports, cilostazol is comparable in safety and efficacy to aspirin and ticlopidine for the prevention of stent thrombosis after implantation. Other off label uses that need more research to determine safety and efficacy include the treatment of bradyarythmias, cerebro-vascular disease and graft vs host disease.

**Indobufen**

Indobufen inhibits platelet aggregation by reversibly inhibiting the platelet cyclooxygenase enzyme thereby suppressing thromboxane synthesis.

The structural formula is:
Clinical trials have evaluated the efficacy of oral indobufen in the secondary prevention of thromboembolic complications in patients with or without atrial fibrillation, in the prevention of graft occlusion after coronary artery bypass graft (CABG) surgery and in the treatment of intermittent claudication. In the secondary prevention of thromboembolic events indobufen 200 mg once or twice daily was significantly more effective than no treatment although not as effective as ticlopidine 250 mg once or twice daily, during 1-year nonblind clinical trials.

In patients with nonrheumatic atrial fibrillation and a recent cerebrovascular event enrolled in the 1-year Studio Italiano Fibrillazione Atriale (SIFA) trial, indobufen 100 or 200 mg twice daily was as effective as warfarin (titrated to produce an international normalized ratio of 2.0 to 3.5) in the secondary prevention of thromboembolic events; the incidences of the composite end-point of major vascular events (10.6 vs 9.0%) and recurrent stroke (5 vs 4%) were similar between treatments. In 2 large 12-month trials, the Studio Indobufene nel Bypass Aortocoronarico (SINBA) and the UK study, indobufen 200 mg twice daily was as effective as aspirin (acetylsalicylic acid) 300 or 325 mg plus dipyridamole 75 mg 3 times daily in the prevention of early and late occlusion of saphenous grafts in patients after CABG surgery. Indobufen 200 mg twice daily for 6 months significantly improved walking capacity compared with placebo, and caused a more pronounced improvement in both pain-free and total walking distance than either pentoxifylline 300 mg or aspirin 500 mg twice daily in separate 6- and 12-month studies of patients with intermittent claudication. Oral indobufen up to 200 mg twice daily was generally well tolerated in >5000 patients with atherosclerotic disease. Adverse events (predominantly gastrointestinal), reported by 3.9% of patients, rarely required withdrawal from treatment. In the SINBA and UK studies, fewer adverse events and less gastrointestinal bleeding were seen with indobufen than with aspirin plus dipyridamole treatment, while in the SIFA trial, noncerebral bleeding events occurred significantly less frequently in indobufen than warfarin recipients (0.6 vs 5.1%) and major bleeding events occurred only in the warfarin group. Conclusion: Indobufen is as effective as warfarin in the prophylaxis of thromboembolic events in at risk patients with nonrheumatic atrial fibrillation, as aspirin plus dipyridamole in the prevention of CABG occlusion and may be more effective than aspirin or pentoxifylline in improving walking capacity in patients with intermittent claudication. The improved tolerability profile of indobufen (favourable gastric tolerance and reduced haemorrhagic complications) compared with aspirin 300 to 325 mg 3 times daily or warfarin, in addition to a similar antiplatelet effect, suggests indobufen can be considered a drug with a definite role in the management of atherothrombotic events. In particular, indobufen may be an effective alternative for at risk patients with nonrheumatic atrial fibrillation in whom anticoagulant therapy is contraindicated or who are at higher risk of bleeding.

Abciximab
Abciximab, a monoclonal antibody, is a potent intravenous blocker of the platelet glycoprotein IIb/IIIa receptor. In addition to its antiplatelets effects, abciximab acts on other receptors, although the clinical significance of these effects is unclear. It has reduced ischemic events after percutaneous coronary intervention (PCI), and its benefit applies to all interventional modalities and all lesion types. It has decreased 1 year mortality, resulting in a high degree of cost effectiveness. The reduction in periprocedural ischemic events, as well as intermediate-term mortality, is particularly robust in diabetic patients. Abciximab has been studied in the medical management of non ST-elevation acute coronary syndromes, with disappointing results and no clear evidence of benefit. However, patients with acute coronary syndromes, when treated by early revascularization, benefit greatly from abciximab. Abciximab as an adjunct to balloon angioplasty or stenting for acute ST-elevation myocardial infarction improves outcomes. Abciximab, in combination with fibrinolytic therapy, is being studied for acute myocardial infarction; phase II studies have been promising, but phase III data are awaited. The study of abciximab for acute stroke and limb ischemia, as well as an adjunct to carotid and peripheral intervention, is in its infancy.

Abciximab (c7E3 Fab) is a monoclonal antibody that consists of a half-human, half-murine chimeric Fab fragment, in which the heavy- and light-chain variable regions from the murine antibody are attached to the constant regions of the human IgG1 and k-chains. It is a powerful antiplatelet agent, likely to decrease clinical thrombosis. Abciximab binds with high affinity to the glycoprotein (GP) IIb/IIIa receptor, although with low specificity. These properties differentiate it from the other intravenous GP IIb/IIIa inhibitors that have been studied. The prolonged platelet inhibition produced by abciximab is another differentiating feature. At 8 days after abciximab bolus and infusion, there is still 29% blockade of the GP IIb/IIIa receptor, owing to reequilibration of aciximab among the circulating platelets.
At 15 days, there remains 13% blockade of the GP IIb/IIIa receptor. This prolonged duration of platelet inhibition, with a gradual recovery, may account for some of the long-term benefit of abciximab that has been noted in clinical practice.

In addition to its antiplatelet effects, mediated by binding to the GP IIb/IIIa receptor, abciximab has another biological action that may be important in reducing thrombosis or inflammation. Abciximab binds to the αβ3 receptor as well as the Mac-1 receptor. These effects of abciximab may influence platelet-leukocyte interactions. The αβ3 receptor, as well as GP IIb/IIIa receptor, appears to play a role in attenuating thrombin generation in response to tissue factor. This effect on thrombin generation may be particularly relevant in conditions such as acute myocardial infarction (MI). In one study of patients with acute MI, abciximab decreased platelet attachment to monocytes, whereas heparin alone did not. Much about the biology of GP IIb/IIIa inhibitors however is not well understood. For example, the contribution of the internal pool of GP IIb/IIIa receptors to platelet aggregation has perhaps been underappreciated. Although abciximab does become internalized, its inhibition of the internal GP IIb/IIIa receptor pool is incomplete, but circulating drug binds externalized receptors.

Abciximab has had a substantial influence on decreasing periprocedural ischemic events and long-term mortality after PCI. The benefit of abciximab is present in both urgent and elective intervention and amplified in acute coronary syndromes. The ability of abciximab to reduce death, MI and urgent revascularization is present across the spectrum of interventional devices utilized, and is complimentary to the benefits of stenting in reducing target vessel revascularization. Diabetic patients especially derive marked benefit from abciximab, with reduction of mortality to the level of placebo-treated nondiabetics. Additionally abciximab is cost-effective in the broad range of patients undergoing PCI. The role, if any, of abciximab for the medical management of acute coronary syndromes without the performance of PCI has not been defined. The usefulness of abciximab in conjunction with primary percutaneous revascularization for acute ST-elevation MI is well established. Large-scale elevation is now underway to define the efficacy of combination therapy with abciximab and reduced dose fibrinolitics for acute MI. The use of abciximab outside of cardiology is likely to grow, particularly for the treatment of cerebrovascular and peripheral arterial diseases.

**Eptifibatide**

It is an antiplatelet drug of the glycoprotein IIb/IIIa inhibitor class. Eptifibatide is a cyclic heptapeptide derived from a protein found in the venom of the southeastern pygmy rattlesnake (Sistrurus miliarius barbouri).

The results of PURSUIT clearly establish a role for eptifibatide as front-line therapy for patients with high-risk acute coronary syndromes. This includes patients with characteristic chest pain, positive cardiac markers (including elevated troponin), or ST segment shifts on the electrocardiogram.

In the settling of percutaneous coronary intervention, the less than expected treatment effect seen with eptifibatide in IMPACT II compared with that seen with abciximab in EPIC and EPILOG may have been a result of under dosing of eptifibatide. The ESPRIT trial, which tested an eptifibatide dosing regimen shown to achieve to achieve more than 80% platelet inhibition, produced highly and statistically significant and clinically relevant reductions in the ischemic clinical complications of this procedure. These benefits were achieved despite the exclusion of subjectively higher-risk patients; patients enrolled in ESPRIT were believed by their physicians not to warrant GP IIb/IIIa receptor blockade as a pretreatment.

All of the trials of eptifibatide used in conjunction with thrombolytic therapy for ST-segment elevation MI have demonstrated trends consistent with improved restoration of coronary perfusion.

**Tirofiban**

Tirofiban is a non-peptide GP IIb/IIIa antagonist that binds reversibly to IIb/IIIa receptors. Its efficacy has been evaluated in many clinical scenarios, including acute coronary syndromes with and without ST elevation, PCI, and as treatment prior to early revascularization. In the PRISM-plus study, which enrolled patients with acute coronary syndromes without persist ST-segment elevation who were treated with intravenous heparin, those randomized to receive torofiban had a lower incidence of death or nonfatal myocardial infarction (MI) at 30 days than those randomized to receive a placebo (8.7 vs. 11.9%, p=0.03). In the PRISM study, which also enrolled patients with non-ST elevation acute coronary syndromes, the 30-day incidence of death or MI was 5.8% in patients randomized to tirofiban, compared with 7.1% in those randomized to heparin (p=0.12), but in patients who had elevated troponin T levels (≥0.1ug/
L06-8 h after presentation, the comparative rates were 13.7 and 3.5% respectively ($p<0.01$). In the RESTORE trial in high-risk patients who underwent angioplasty, tirofiban reduced the combined 30-day incidence of death, MI, or urgent revascularization from 10.5 to 8.0% ($p=0.052$)\(^7\).

In the TACTICS-TIMI-18 trial, 4-48h of tirofiban treatment followed by early revascularization was compared with early conservative strategy in patients with non-ST elevation acute coronary syndromes and reduced the 6-month incidence of death, MI, or severe angina requiring hospitalization from 26.3 to 16.4% ($p=0.006$) in patients with $\geq 0.5$mm of ST-segment depression and from 24.2 to 14.3% ($<0.001$) in patients with elevated troponin levels.

The TARGET trial compared tirofiban with abciximab in patients undergoing percutaneous coronary intervention for an acute coronary syndrome or stable angina. The primary endpoint of death, MI or urgent target-vessel revascularization within 30 days occurred in 7.5% of those who received tirofiban versus 6% of those who received abciximab ($p=0.037$).

Clinical trials using angiographic assessment have also been performed to evaluate the efficacy and safety of tirofiban in conjunction with low-molecular-weight heparin, and patients receiving fibrinolytics agents for ST-elevation acute coronary syndromes. It is now established that tirofiban is effective and safe for patients presenting with non-ST-elevation acute coronary syndromes, whether it is used as part of a conservative medical strategy or as treatment before revascularization procedures.

REFERENCES
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