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Review

Oral Platelet Glycoprotein IIb/IIIa Receptor Inhibitors—Part II

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Summary: Although the hypothesis of benefit from prolonged oral IIb/IIIa inhibition was appealing, the large Phase III trials have uniformly shown there was no improvement in outcome. In addition, there was an increased mortality seen in patients treated with the oral IIb/IIIa inhibitor. This latter finding is not adequately explained, but is likely a multifactorial problem of this strategy of platelet inhibition. The trials found that, even with no improvement in efficacy, there was increased bleeding, meaning that for chronic therapy with IIb/IIIa inhibition there does not appear to be a therapeutic window. Accordingly, chronic oral IIb/IIIa inhibition appears to have been well tested but has not worked. Fortunately, there are several other oral antiplatelet agents available that have shown beneficial results, including clopidogrel. In addition, other newer classes of antiplatelet agents are in earlier stages of development. Thus, agents targeted more "upstream" in platelet activation pathways may offer a more tolerable and efficacious approach to long-term antiplatelet therapy.

Key words: platelets, acute coronary syndromes, myocardial infarction, unstable angina, antiplatelet therapy, prognosis, angioplasty

Introduction

With the numerous positive trials with glycoprotein (GP) IIb/IIIa inhibitors given intravenously,[1] it was hoped that one could extend the benefit of GP IIb/IIIa inhibition to long-term treatment. Part I of this article reviewed the pharmacology and initial dose-ranging experience of the various oral IIb/IIIa inhibitors.

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Large Phase III Trials

There have been six Phase III trials conducted with oral IIb/IIIa receptor blockers, all with very disappointing results. Newby *et al.* have summarized the results of the first four trials,[2] the Orbofiban in Patients with Unstable Coronary Syndromes—Thrombolysis in Myocardial Infarction 16 (OPUS-TIMI 16) trial,[3] the Evaluation of oral Xemilofiban In Controlling Thrombotic Events (EXCITE) Trial,[4] and the two Sibrafiban versus aspirin to Yield Maximum Protection from ischemic Heart events post-acute cOroNary sYndromes (SYMPHONY) trials.[5, 6] A fifth trial, Blockade for the GP IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO), was stopped prematurely because of an increase in mortality, but the full results of this study have not been released. A sixth study (Peripheral arterial disease Utilization of Roxifiban for the Prevention Of iSchemic Events [PURPOSE]) with roxifiban[7] was also terminated early because of excess bleeding.

The first Phase III trial of an oral II/IIIa inhibitor in patients with acute coronary syndromes was the OPUS-TIMI 16 trial. This trial involved 10,288 patients randomized at 888 hospitals in 28 countries worldwide.[3] The inclusion criteria were onset within the last 72 h of an acute coronary syndrome defined as rest ischemic pain lasting at least 5 min associated with either electrocardiographic (ECG) changes, positive cardiac enzymes, or a prior history of vascular disease. Major exclusion criteria included renal insufficiency (creatinine > 1.6 mg/dl or an estimated creatinine clearance of < 40 cc/min), increased bleeding risk, or need for warfarin.

Eligible patients were treated with 150–162 mg of aspirin and were randomized, in double-blind fashion, to one of two dosing strategies of orbofiban given twice daily, or placebo. In one dose, orbofiban was given 50 mg twice daily throughout the trial (50/50 group), in the other, the 50 mg twice daily dose was given for the first 30 days (the highest risk period), and then the dose was reduced to 30 mg twice daily (50/30 group). Other medical and interventional therapy was at the discretion

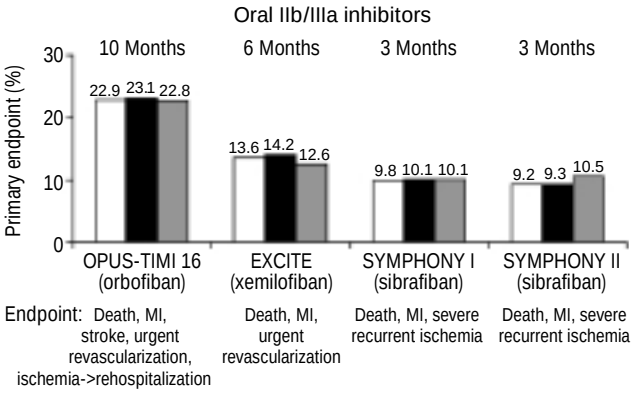

FIG. 6 Primary composite outcomes in the four large Phase III trials with available data. Data from Refs. 3, 4, 5, and 6. MI = myocardial infarction. □ = Aspirin, ■ = low dose, ▩ = high dose. OPUS-TIMI 16 = Orbifan in Patients with Unstable Coronary Syndrome-Thrombolysis in Myocardial Infarction 16, EXCITE = Evaluation of oral Xemilofiban in Controlling Thrombotic Events, SYMPHONY = Sibrafan versus aspirin to Yield Maximum Protection from ischemic Heart events post-acute cOroNary sYndromes.

of the treating physician. Patients were seen at 14 and 30 days and every 3 months. The primary endpoint was a composite of death, myocardial infarction (MI), recurrent ischemia leading to rehospitalization or urgent revascularization, or stroke. The planned sample size was to be 12,000 patients, but the trial was stopped prematurely after an unexpected finding of increased mortality at 30 days was observed in one of the orbofiban groups.

The rate of the primary composite endpoint of death, MI, recurrent ischemia leading to urgent revascularization or rehospitalization, or stroke at 30 days was 10.7% for placebo versus 9.5% for orbofiban (p = 0.05).[3] Mortality at 30 days was low, 1.4%, in the placebo group, but higher, 2.3%, in the 50/30 group, and 1.6% in the 50/50 group. Kaplan-Meier event rates to 300 days were 20.5% for placebo, 20.2% in the 50/30 group, and 19.5% in the 50/50 group (p = NS) (Fig. 6; for Figs. 1–5, see Part I). Mortality through 10 months was 3.7% for the placebo group versus 5.1% in the 50/30 group (p = 0.008), and 4.5% in the 50/50 group (p = 0.11) (Fig. 7). There was a higher rate of major hemorrhage with orbofiban: it occurred in 2.0%, 3.7% (p = 0.0004), and 4.5% (p < 0.0001) of patients in the placebo, 50/30, and 50/50 groups, respectively. The rate of thrombocytopenia was low, 0.6%, but significantly higher than placebo (0.1%), p < 0.001.

Exploratory substudies were analyzed to try to understand the increased mortality. Two substudies from OPUS-TIMI 16 found that orbofiban led to increases in measures of platelet activation, notably P selectin and fibrinogen binding (Fig. 8).[8,9] These data are consistent with other observations with other agents, which induced an apparent prothrombotic effect with increases in measures of platelet activation and in platelet aggregation when drug levels were low[10] (see also below).

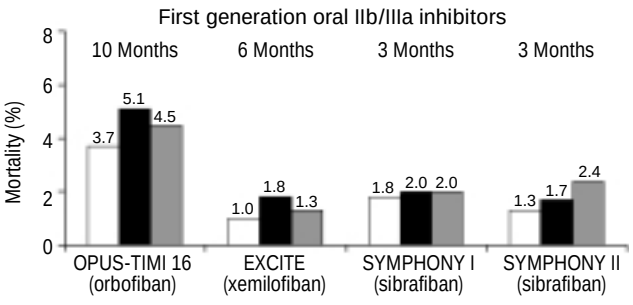

FIG. 7 Mortality in the four large Phase III trials with available data (data from references cited in Fig. 6). □ = Aspirin, ■ = low dose, ▩ = high dose. Trial acronyms as in Fig 6.

EXCITE Trial

The EXCITE trial studied xemilofiban in 7,232 patients undergoing percutaneous coronary intervention (PCI) with either balloon angioplasty or stenting without adjunctive intravenous IIb/IIIa inhibition. Patients were randomized in a double-blind fashion to receive one of two doses of xemilofiban, or placebo: all patients treated with xemilofiban received a first dose of 20 mg 30 to 90 min prior to PCI, followed by either 10 or 20 mg three times daily for 6 months.[11]

The primary endpoint was death, MI, or urgent revascularization through 6 months. This occurred in 13.6% of patients in the placebo group, 14.1% of patients in the xemilofiban 10 mg group, and in 12.6% of patients in the xemilofiban 20 mg group (p = NS).[11] There were slightly fewer periprocedural MIs over the first 48 h following PCI, but this benefit was not sustained at 30 days or 6 months.[11] Mortality at 6 months was 1.0% for placebo, 1.6% for the 10 mg xemilofiban dose group, and 1.1% for the 20 mg dose group.[11] Major bleeding was significantly more common in the patients treated with xemilofiban.[11] Thus, xemilofiban did not significantly reduce cardiac events in this patient population.

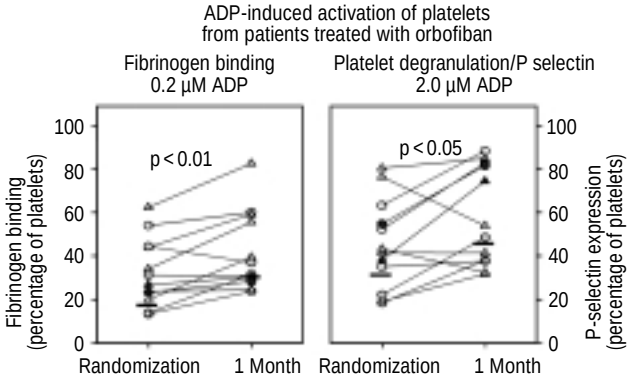

FIG. 8 OPUS-TIMI 16 Substudy: Increases in measures of platelet activation following treatment with the oral IIb/IIIa inhibitor orbofiban. Adapted from Ref. No. 8 with permission. ADP = adenosine diphosphate.

SYMPHONY I

Following the Phase II trial of sibrafiban (TIMI 12),[12] the first SYMPHONY trial was a large double-blind, aspirin-controlled trial of two regimens of sibrafiban for the treatment of patients stabilized following an acute coronary syndrome.[5] A total of 9,233 patients with either acute MI or high-risk unstable angina (with ST deviation of ≥ 0.5 mm), who were clinically stable for at least 12 h, were randomized to receive either aspirin (80 mg twice daily) or one of two doses of sibrafiban (without aspirin) every 12 h for a total of 3 months. The dose of sibrafiban was either 3, 4.5, or 6 mg based on body weight and renal function. The primary endpoint was a composite of death, MI, and severe recurrent ischemia.

There was no difference in the primary endpoint between aspirin (9.8%), low-dose sibrafiban (10.1%), and high-dose sibrafiban (10.1%).[5] The individual components of the endpoint were also not different between the groups. There was a higher rate of major bleeding with sibrafiban at both the high (5.7%) and low (5.2%) doses compared with aspirin (3.9%).[5] In conclusion, sibrafiban without aspirin was not superior to aspirin for prevention of cardiac events following acute coronary syndromes.

SYMPHONY II

The second SYMPHONY trial, which was terminated prematurely when the SYMPHONY 1 results were available, compared the combination of low-dose sibrafiban plus aspirin versus high-dose sibrafiban (without aspirin) versus aspirin alone in 6,671 patients with stabilized acute coronary syndromes.[6] With an average follow-up of 90 days, death, MI, or severe recurrent ischemia was not different among the three groups: 10.5% in the high-dose sibrafiban group, 9.2% in the low-dose sibrafiban plus aspirin group, versus 9.3% in the group receiving aspirin alone.[6] In this trial (but not in SYMPHONY 1), mortality was significantly higher in the high-dose sibrafiban group: 2.4 versus 1.7% in the low-dose sibrafiban plus aspirin group versus 1.3% for placebo. Recurrent MI followed a similar pattern: 6.9% for high-dose sibrafiban, 5.3% for low-dose plus aspirin, and 5.3% for aspirin alone. Major bleeding was more common in the two sibrafiban groups: 4.6% in the high-dose group, and higher still for the combination of low-dose sibrafiban plus aspirin (5.7%) versus 4.0% for aspirin.

BRAVO

Lotrafiban was evaluated in the Blockade for the GP IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO) trial, in which all patients received aspirin and were randomized to lotrafiban or placebo. The BRAVO study differed from the other studies of oral GP IIb/IIIa blockers in that it was the first trial to include neurological patients. Of approximately 9,200 enrolled, 60% had an acute coronary syndrome and 40% suffered either an ischemic stroke or transient ischemic attack (TIA).

The trial was stopped early by the data and safety monitoring committee after an interim analysis demonstrated that lotrafiban was associated with an increased mortality compared with placebo (2.7 vs. 2.0%, $p = 0.022$).[13] Furthermore, lotrafiban was associated with increased rates of serious thrombocytopenia (2.2 vs. 0.5%, $p < 0.0001$) and major bleeding (4.2 vs. 1.3%, $p < 0.0001$).

Roxifiban

Roxifiban has many characteristics that distinguish it in the class of oral IIb/IIIa inhibitors, with features that appear to overcome the pharmacologic deficiencies of the reversible oral IIb/IIIa inhibitors (Fig. 2; see Part I). Most important, roxifiban binds tightly to platelet receptors and is slow to dissociate.[14–17] The half-life of dissociation is 7 min, more than 40 times longer than the "short-acting" molecules such as tirofiban (approximately 10–20 s).[16] Roxifiban's tight binding is similar to that of abciximab, which also has a long half-life of dissociation.[16] This prolonged antiplatelet effect would avoid the possibility of "on-off" proaggregatory effects of the drug binding to the IIb/IIIa inhibitor,[10] which may explain some of the findings from previous trials with oral IIb/IIIa inhibitors. Indeed, experimental models have shown that roxifiban has superior antithrombotic effects compared with other "short-acting" IIb/IIIa inhibitors.[14] With its long-half life, roxifiban is administered once daily. With its high potency, the oral doses needed are only 0.5–1.5 mg once daily. It has a very stable antiplatelet effect over time (i.e., a low peak-to-trough level of platelet inhibition) and blood levels do not appear to be affected significantly by renal function. Thus, with its long half-life and low "peak to trough" levels of platelet inhibition, it has a very stable antiplatelet effect over time. It has shown promise in a large phase II trial of patients with stabilized acute coronary syndromes.[18]

The PURPOSE trial evaluated roxifiban plus aspirin versus aspirin alone in patients with moderate to severe peripheral arterial disease, defined as either claudication and ankle-brachial index < 0.60 or critical limb ischemia.[19] Patients were randomized to receive long-term treatment with roxifiban (1.5 mg/day) plus aspirin, compared with aspirin alone (75–325 mg). The primary endpoint was a composite endpoint of death, nonfatal MI, or nonfatal stroke. After randomization of 355 patients during 6 months, the study was stopped because of excess bleeding. The median level of inhibition of platelet aggregation (IPA) was 81% for roxifiban and 10% for placebo.[19] Death occurred in four (2.3%) patients on roxifiban and two (1.1%) patients on placebo (p = NS); MI occurred in one (0.6%) versus three (1.7%) patients, respectively (p = NS). The rate of severe/major bleeding during roxifiban use was 5.7 versus 1.1%, and was much higher than that observed in other trials of antithrombotic drugs. Thrombocytopenia occurred in 2.3% of roxifiban-treated patients.[19]

Thus, this trial tested the hypothesized best approach for efficacy—to have a high level of inhibition, with a steady level of inhibition over the day. While there were numerically fewer events in the roxifiban group, the number of patients

and events was too small to tell whether this had a favorable effect on efficacy or an adverse effect on mortality. However, based on the high rate of major bleeding, it is clear that this high level of inhibition was not tolerated by the patients. Thus, long-term, high degrees of IIb/IIIa receptor blockade do not appear tolerable.

Other Agents Tested in Phase I and II Trials

Two agents to date have been evaluated as both intravenous and oral compounds, klerval,[20] and (le)fradafiban.[21] In the TIMI 15 B trial, a transition from initial intravenous (IV) treatment to prolonged oral treatment with klerval was able to achieve a smooth transition in the level of platelet inhibition in patients with acute coronary syndromes.[20] However, because of low bioavailability, the development of this drug was discontinued. Lefradafiban (oral) and fradafiban (IV) await further testing. Lefradafiban has been tested in a dose-ranging trial, the Fibrinogen Receptor Occupancy STudy (FROST),[22] with an intriguing trend toward benefit among patients with a positive troponin T,[22] which parallels the findings seen with intravenous IIb/IIIa inhibitors.[23, 24] This suggests that identification of the ideal patients with risk stratification methods (clinical factors, ST deviation, and cardiac markers) might assist in targeting these agents to appropriate patients. Cromofiban is another agent with a very long half life (approximately 24 h) for which preliminary information has shown stable levels of platelet inhibition, but it has not been developed given the failure of this class of drugs.

Meta-Analysis of Oral Glycoprotein IIb/IIIa Inhibitors

Two meta-analyses of the large trials have been published, involving more than 33,000 patients from OPUS-TIMI 16, EXCITE, and SYMPHONY I and II. The first revealed a statistically significant increase in mortality with oral GP IIb/IIIa inhibitor therapy (odds ratio [OR] 1.37; 95% confidence interval [CI] 1.13–1.66; $p = 0.001$).[25] This effect was seen regardless of whether aspirin was coadministered and/or regardless of GP IIb/IIIa inhibitor dose. Analyses of other endpoints suggest that prolonged oral GP IIb/IIIa inhibitor therapy is associated with no change in the rate of MI (OR 1.04; 95% CI 0.93–1.16; $p = 0.48$), but an apparent reduction in the need for urgent revascularization (OR 0.77; 95% CI 0.66–0.87; $p < 0.001$). There was a clear increase in major bleeding (OR 1.74; 95% CI 1.52–2.00; $p < 0.001$).

A more recent meta-analysis had similar findings and noted that the adverse effect on mortality was remarkably consistent across these large trials despite differences in the patients studied and the design of the trials.[2] In none of the studies was any benefit seen on the composite endpoint of death, recurrent MI, or other recurrent ischemic events. However, another unfortunate consistency was that there was a higher mortality rate in patients receiving the oral IIb/IIIa inhibitors, with a 30–35% increase in the OR even when including the BRAVO trial.[2, 26]

Potential Mechanisms for Increased Mortality

One of the leading explanations for the poor outcomes and increased mortality is variability in the pharmacokinetics and pharmacodynamics of the orally administered IIb/IIIa inhibitors. As has been described in the Phase II dose-ranging trials in which platelet aggregation studies were undertaken, the level of platelet inhibition varies widely from patient to patient and within an individual patient over the time of the dosing interval.[27–30] Thus, some patients may have levels of inhibition and platelet aggregation as low as zero, while others may have levels of inhibition approaching 100% (Fig. 3; see Part I). With such variability, it is not hard to understand why there would be lack of a consistent benefit in patients treated with these oral agents at the dosing strategies used.

Prothrombotic Hypothesis

Another potential explanation is that the oral IIb/IIIa inhibitors may have created a paradoxical prothrombotic tendency and thus increased the risk of recurrent thrombotic events. This was first seen in the OPUS-TIMI 16 trial and confirmed in the second SYMPHONY study. In support of this hypothesis, substudies within OPUS-TIMI 16 have documented increases in P-selectin and CD-63, both markers of platelet activation (Fig. 8).[8, 31] In vitro studies by Peter *et al.* have shown that binding of a IIb/IIIa receptor blocker and then dissociation of this blocker from the receptor can leave the IIb/IIIa receptor open for binding from fibrinogen, which then could lead to a paradoxical increase in platelet aggregation following treatment with a IIb/IIIa receptor blocker, especially at times when the levels were low (Fig. 9).[10] Since the variability in dosing is so marked with the oral agents, this became a very attractive hypothesis for why increased thrombotic deaths were seen in several of the oral IIb/IIIa inhibitor trials. It is noteworthy that this has not been seen for all agents; thus, there is a potential that some agents, notably orbofiban, may lead to an increased propensity for this prothrombotic effect.

Newby *et al.* have listed other explanations such as a proinflammatory effect,[26] or other effects mediated by apoptosis,[2] that may play a role in increasing adverse events with this class of drugs. Recent studies have found a dose-dependent increase in caspase-3 expression and apoptosis when RGD peptides, xemilofiban, or orbofiban were incubated with cardiomyocytes; this effect was not seen with eptifibatide or abciximab, suggesting that it is specific to the RGD peptides.[32] This appears to be one potential explanation for increased mortality outside the prothrombotic hypothesis. The bottom line is that this is likely a multifactorial problem.

Conclusion

Although the hypothesis of benefit from prolonged oral IIb/IIIa inhibition was appealing, it appears that the balance between efficacy and safety has left a therapeutic window that is 0. On one hand, efficacy was poor and mortality increased

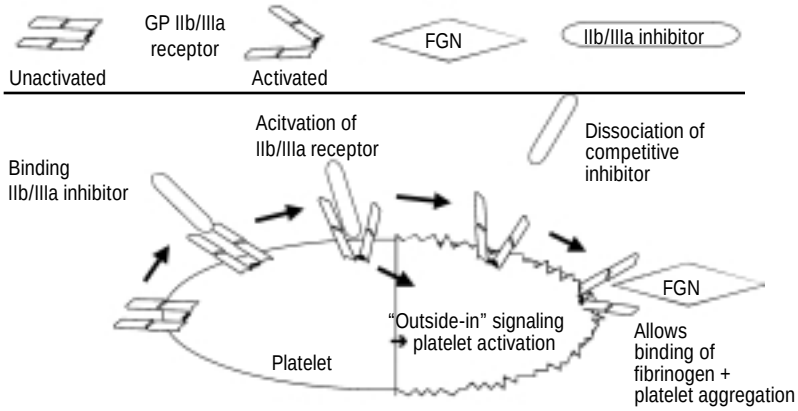

FIG. 9 Depiction of the potential for platelet activation by binding of IIb/IIIa inhibitor to the receptor. As shown, if the IIb/IIIa inhibitor binds to the receptor, changes in the receptor occur, with changes in the conformation of the receptor to the activated state, and "outside-in" signaling leads to activation of the platelet. However, if the IIb/IIIa inhibitor dissociates (e.g., when plasma levels fall to low levels) the receptor is left in the activated position and fibrinogen can bind and lead to an increase in platelet aggregation. Adapted from Ref. No. 10 with permission. FGN = fibrinogen.

(as did bleeding) when levels of platelet inhibition were low, but when a higher, steady level of inhibition was achieved, major bleeding was even higher, at unacceptable levels. Thus, there does not appear to be a window at all for long-term IIb/IIIa inhibition. Accordingly, chronic oral IIb/IIIa inhibition appears to have been well tested but has not worked. One potential is that the oral IIb/IIIa inhibitors might be a more inexpensive means of short-term therapy. However, given the importance of a high level of inhibition to achieve optimal outcomes, the inherent variability of an oral drug might make this difficult. Formal dosing studies would have to establish a dosing strategy that achieves high and steady levels of inhibition. Fortunately, there are several other oral antiplatelet agents available that have shown promise, the most notable being clopidogrel and the thienopyridines. Other classes of agents that may offer a more tolerable and efficacious approach to long-term antiplatelet therapy are also in early development.

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