INDIAN HEART JOURNAL XXX (2012) 1–4

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Editorial

PAR-1 inhibitor antiplatelet agents: Performance below par?

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1. Antiplatelet therapies and acute coronary syndrome

Antiplatelet agents reduce mortality from acute coronary syndrome (ACS). Aspirin, clopidogrel, glycoprotein IIb/IIIa inhibitors and newer agents such as prasugrel or ticagrelor are now used routinely in ACS and with percutaneous coronary intervention (PCI). Although currently available antiplatelet therapies are highly effective, they cannot nullify atherothrombotic risk. Recurrent ischaemic events occur despite treatment with aspirin and/or clopidogrel, the most widely prescribed antiplatelet drugs.[1] Breakthrough ischaemic events may reflect the inability of these agents to fully suppress the stimulus for platelet activation at sites of plaque disruption, or they may be the result of resistance to the antiplatelet effects of aspirin or clopidogrel.[2] Aggressive risk factor profiles, genetic background and a heightened thrombotic state can all play a part in the recurrence of ischaemic events.

One of the most feared complications in patients with ACS undergoing PCI is stent thrombosis (ST), which has an unacceptably high mortality rate of about 45%.[3] The rate of stent thrombosis remains high even in the newer studies where state-of-the-art antiplatelet therapy was deployed. For instance, in the Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38 trial of prasugrel, the rates of stent thrombosis in the patients treated with prasugrel and clopidogrel were 1.1% and 2.4%, respectively at 450 days follow-up.[4] The Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) and Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trials confirmed that the underlying rate of stent thrombosis in patients with ACS undergoing PCI can be as high as 2%–3%.[5,6] This has led to major research efforts to find the consummate antiplatelet agent; one that would have a rapid onset of action, deliver complete platelet blockade, be fully reversible and provide optimal anti-ischaemic effects in the absence of an increase in bleeding risk.

2. What are PAR-1 inhibitors?

Protease-activated receptor-1 (PAR-1) inhibitors are a new class of antiplatelet agents which affect platelets via pathways that are different from that of currently used agents. Whilst aspirin acts on platelets via the thromboxane pathway and clopidogrel, prasugrel and ticagrelor act via inhibition of the platelet adenosine diphosphate (ADP) receptor $P2Y_{12}$, PAR-1 inhibitors target thrombin-induced platelet aggregation. Thrombin, a serine protease is the most potent physiological agonist of platelets and responsible for the generation of fibrin. Thrombin receptor signalling in platelets is mediated by protease-activated receptors (PARs) PAR-1 and PAR-4, which are essentially G-protein-linked members of the 7-transmembrane domain receptor superfamily.[7] PAR-1 is activated by subnanomolar concentrations of thrombin and is likely the primary platelet thrombin receptor in humans.[8] Vorapaxar and atopaxar are the two main PAR-1 inhibitors that have been evaluated in clinical studies. Vorapaxar has been shown to selectively and potently inhibit thrombin-induced platelet aggregation in experimental studies.[9,10] Atopaxar has been shown to have synergistic effects with aspirin and a combination of aspirin and clopidogrel in human volunteers.[11]

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0019-4832/$ – see front matter
http://dx.doi.org/10.1016/j.ihj.2012.09.003

Please cite this article in press as: Natarajan A, et al., PAR-1 inhibitor antiplatelet agents: Performance below par?, Indian Heart Journal (2012), http://dx.doi.org/10.1016/j.ihj.2012.09.003

3. Vorapaxar

Vorapaxar (SCH 530348; Merck, Whitehouse Station, NJ, USA) is rapidly absorbed following oral administration, has high bio-availability and results in potent, selective and reversible PAR-1 inhibition.[12] The phase 2 programme of vorapaxar consisted of three randomized trials. The first, in patients with stable coronary artery disease (CAD) undergoing elective PCI, the TRA-PCI[13] and two studies in Japanese patients with ACS or a history of stroke.[14,15] In TRA-PCI, of the 1030 patients undergoing PCI, nearly all were on aspirin and clopidogrel and randomized to receive one of three doses of vorapaxar or placebo. The primary endpoint of Thrombolysis In Myocardial Infarction (TIMI) major and minor bleeding was similar between the vorapaxar and placebo arms. The platelet substudy of TRA-PCI showed dose-dependent platelet inhibition.[13] The composite ischaemic endpoint was numerically lower in the pooled vorapaxar groups, mainly due to a reduction in PCI-related myocardial infarction (MI). The Japanese ACS study demonstrated the outcomes that were similar to the TRA-PCI trial.[14] The Japanese stroke study was a small one with 90 patients in which few overall events were documented.[15] These studies served as impetus for two phase 3 studies of vorapaxar that are discussed below.

3.1. *Vorapaxar in acute coronary syndrome*

Vorapaxar was tested in the phase 3 Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial in which it was compared against placebo in nearly 13,000 patients presenting with Non-ST-segment Elevation Acute Coronary Syndrome (NSTE-ACS).[16] Most of the patients in the study were already on dual antiplatelet therapy at entry. The study was terminated early after a safety review, owing to a significantly increased incidence of bleeding including intracranial haemorrhage in the vorapaxar arm. After a median follow-up of 502 days, there was no difference in the incidence of the composite primary endpoint of death from cardiovascular causes, MI, stroke, recurrent ischaemia with rehospitalisation, and/or urgent coronary revascularization, between the two arms (2-year cumulative event rate, 18.5% vs 19.9%; hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.85–1.01; $P = 0.07$). Death from cardiovascular causes occurred less frequently in the vorapaxar compared to placebo group (14.7% and 16.4%, respectively; HR, 0.89; 95% CI, 0.81–0.98; $P = 0.02$). Rates of moderate and severe bleeding were significantly higher with vorapaxar compared to placebo (7.2% vs 5.2%; HR, 1.35; 95% CI, 1.16–1.58; $P < 0.001$). In addition, incidence of intracranial bleeding was higher with vorapaxar (1.1% vs 0.2%; HR 3.39; 95% CI, 1.78–6.45; $P < 0.001$).[16]

To put this in perspective, there was an absolute excess at two years of two moderate or severe bleeds, approximately one additional intracranial haemorrhage, and about five Thrombolysis In Myocardial Infarction criteria (TIMI) clinically relevant bleeds for every 100 patients treated. The trial was therefore terminated early due to this unacceptable high bleeding incidence. And the bleeding risk came with the additional drawback of a failure to achieve a reduction in the primary endpoint. The increased bleeding was thought to be secondary to an interaction between vorapaxar and thienopyridine, but the evidence for this was not striking.

3.2. *Vorapaxar in secondary prevention*

The other large phase 3 vorapaxar trial was the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2P)-Thrombolysis In Myocardial Infarction (TIMI) 50 trial, that was published slightly ahead of the TRACER trial.[17] Over 26,000 patients with a history of recent MI (67% of study population), ischaemic stroke or transient ischaemic attack (19%), or peripheral arterial disease (14%) within the preceding 2 weeks to 12 months, were randomized to receive vorapaxar or placebo.[17] After 2 years, the data and safety monitoring board recommended discontinuation of the study treatment in patients with a history of stroke due to an unacceptably high risk of intracranial haemorrhage. The study was however, allowed to be continued in the rest of the patients.

At 3 years follow-up, the primary endpoint had occurred in 1028 patients (9.3%) in the vorapaxar group and 1176 patients (10.5%) in the placebo group (HR, 0.87; 95% CI, 0.80–0.94; $P < 0.001$). The pre-specified secondary endpoints of cardiovascular death, MI, stroke, or recurrent ischaemia leading to revascularization also occurred less frequently with vorapaxar arm compared to placebo – 1259 patients (11.2%) versus 1417 patients (12.4%) (HR, 0.88; 95% CI, 0.82–0.95; $P = 0.001$). The ischaemic reduction was most pronounced in the patients with prior MI.[17]

But these endpoint reductions came at the cost of increased bleeding; nearly all measures of major bleeding were increased in the vorapaxar arm of the trial. Moderate or severe bleeding as per the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria was higher with vorapaxar (4.2% vs 2.5%, HR 1.66; 95% CI 1.43–1.93; $P < 0.001$). TIMI clinically significant bleeding (15.8% vs 11.1%, HR 1.46; 95% CI 1.36–1.57; $P < 0.001$) and intracranial bleeding (1% vs 0.5%, HR 1.94; 95% CI 1.39–2.70; $P < 0.001$) were also significantly higher with vorapaxar compared with placebo.[17]

Use of dual antiplatelet therapy beyond one year following ACS events can be fraught with complications. The patients in the TRA 2P-TIMI 50 had suffered recent atherothrombotic events. Accordingly, the vast majority of them were already on dual antiplatelet therapy; many on thienopyridines and other agents such as dipyridamole were also used at the individual clinicians' discretion. Hence adding vorapaxar on top of conventional antiplatelet treatment and continuing the same beyond one year could have heightened the bleeding risk. Indeed, the large Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial that was conducted in the previous decade, failed to find benefit for dual aspirin and clopidogrel therapy for secondary prevention beyond one year.[1]

The trialists argued that for the group with no prior history of stroke and body weight over 60 kg, vorapaxar offered net benefit. For this group, the number needed to treat to prevent one event was 53 and the number needed to cause a severe bleed or intracranial haemorrhage were comparatively high at

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333 and 500 respectively. Nevertheless, the fact that there were 148 fewer adverse cardiovascular events and 171 greater moderate or severe bleeds, including 49 instances of intracranial bleeding in the trial, scored against vorapaxar.

The US Food and Drugs Administration (FDA) is yet to pass its judgement on Vorapaxar. The UK National Institute of Health and Clinical Excellence (NICE) has not reviewed this drug as yet.

4. Atopaxar

Atopaxar (E5555, Eisai, Co. Ltd, Tokyo, Japan) is a potent and reversible PAR-1 inhibitor. Its actions are more rapidly reversible compared to vorapaxar. Atopaxar was tested in a large phase 2 programme called LANCELOT which comprised four cohesive trials with a common endpoint-definition. The first two were conducted in Japanese patients with ACS ($n = 241$) and CAD ($n = 263$) respectively.[18] Patients were already on aspirin and randomized to receive varying doses of atopaxar following loading versus placebo. Bleeding according to the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) scale was similar between the pooled vorapaxar and placebo groups. Non-major TIMI bleeding was numerically higher with the highest used dose of atopaxar. The other two trials LANCELOT-ACS ($n = 603$) and LANCELOT-CAD ($n = 720$) were similarly designed but had larger study populations.[19,20] In the LANCELOT-ACS trial, CURE major bleeding was numerically higher in the atopaxar group versus placebo, whereas incidence of ischaemic endpoints was similar between the two arms.[19] In the LANCELOT-CAD study in which patients were treated for 24 weeks and had a further 4-week follow-up, outcomes were slightly different.[20] Rates of bleeding were significantly higher with atopaxar-treated patients as measured by CURE (3.9% vs 0.6%; $P = 0.03$) and TIMI criteria. This bleeding risk was observed to be dose-dependent. Ischaemia-related events were only numerically lower in those treated with atopaxar. Interestingly, in all four LANCELOT studies atopaxar showed a dose-dependent increase in liver function abnormality and prolongation of QTc interval, but without reported symptoms. Taken as a whole, higher doses of atopaxar although resulted in improved platelet inhibition, increased bleeding risk. The reduction in ischaemic endpoints during the short follow-periods in the studies was not convincing. The outcomes from these phase 2 studies were therefore not resoundingly positive, but large phase 3 trials will clearly be required to determine the true clinical impact of atopaxar.

5. Conclusion

As currently established antiplatelet therapy cannot nullify the risk of recurrent ACS, the search has been ongoing for the consummate antiplatelet agent, one that would effectively negate risk without increasing bleeding incidence. PAR-1 inhibitors are a novel class of antiplatelet agents that have been developed over the last two decades. Of the two clinically tested PAR-1 inhibitors, vorapaxar has undergone testing in phase 3 trials whereas atopaxar remains at the phase 2 stage. Although vorapaxar showed some promise in phase 2 studies, the two large phase 3 trials delivered disappointing results, primarily due to an increased risk of bleeding. Indeed, this led to the premature termination of one of the two phase 3 trials – the trial in patients with ACS. Surprisingly, there was a reduction in ischaemic endpoints when vorapaxar was used for secondary prevention but not when used in the acute stages of ACS. The clear and present bleeding risk and lack of endpoint reduction in ACS, does not bode well for vorapaxar. This future of this innovative class of antiplatelet drugs, which was once held to be bright, now seems to have turned a deep shade of grey.

Funding

Not applicable.

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