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Research Article

TO STUDY THE CLINICAL USES AND ASSOCIATED RISKS OF TYPE 1 PROTEASE ACTIVATED RECEPTOR ANTAGONISTS

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ABSTRACT

Antiplatelet therapy is the mainstay in inhibiting the over activation of platelets in myocardial infarction, stroke, ischemia etc. Thrombin is the most potent platelet agonist and is involved in thrombus development in vessels. It has two receptors on human platelets, Protease Activated Receptor (PAR) 1 and 2. The drugs that inhibit PAR 1, e.g. vorapaxar and atopaxar have antithrombotic effects and were proposed to have less hemorrhagic complications. However, various clinical trials show that these drugs can be safely used only in a specific population group. More trials are needed before these drugs are approved for use in patients with thrombotic complications.

Key Words: *Vorapaxar, Atopaxar, Thrombosis, Bleeding, Antiplatelet, Thrombin Receptor Antagonists*

INTRODUCTION

Platelets are the key players in both physiological and pathological thrombosis and haemostasis. Pathological thrombosis can lead to problems like Myocardial Ischemia, Stroke etc. Hence, antiplatelet drugs have found their immense use in such patients, preventing the pathological thrombosis and thereby decreasing the associated morbidity and mortality (Xiang *et al.,* 2008). Thrombin is a very strong agonist for platelet activation and acts through its two Protease Activated Receptors (PAR 1&4) present on the surface of human platelets. PAR 1 is a major human platelet receptor and has 10-100 times more affinity for thrombin compared to PAR 4 (Coughlin, 2005). Therefore drugs which target and inhibit PAR1 will have strong antiplatelet effects. Oral selective PAR 1 antagonists currently under scanner are vorapaxar and atopaxar. The preclinical studies have demonstrated their safety and efficacy as novel antiplatelet agents (Diego *et al.,* 2011).

Vorapaxar is given orally & rapidly absorbed, with high bioavailability,>90%. It dissociates from the PAR-1 receptor slowly, thereby having a slow elimination, with half life of approximately 160-300 hours. Hence it has a prolonged effect (Becker *et al.,* 2009). Vorapaxar is extensively metabolized by CYP3A4, therefore, co administration of drugs that modify the metabolic activity of CYP3A4 e.g. rifampicin and ketoconazole could potentially modulate vorapaxar plasma levels (Morrow *et al.,* 2009). Atopaxar is also orally active PAR-1 antagonist, exhibiting a slower onset of action *i.e.,* 3.5 h and lower half-life (23 h), compared with vorapaxar. Like vorapaxar, it is also metabolized by CYP3A4 (Ueno *et al.,* 2010). The effect of vorapaxar lasts longer on the platelet function as compared to that of atopaxar after its withdrawal.

However, the phase 3 clinical trial for vorapaxar and phase 2 clinical trial of atopaxar the drugs didn't meet the expectations as vorapaxar was seen to have good efficacy but with an associated higher bleeding risk, especially in stroke patients and atopaxar was hepatotoxic, leading to the drop in development of latter (Kallirroi *et al.,* 2012). The subgroup analysis of phase 3 trial of vorapaxar however points towards the feasible use of this drug clinically in a carefully chosen population, with a better efficacy as compared to the available antiplatelet drugs, alone or in combination with older antiplatelets like aspirin, with less bleeding risks (David *et al.,* 2012).

MATERIALS AND METHODS

The present study analyzed the spectrum of clinical use and associated risks of vorapaxar and atopaxar, in patients with cardiovascular disorders like myocardial infarction, stroke, ischemia, by reviewing various studies. Searches were conducted using the databases like Pubmed, Cochrane library, Wiley online library and Medscape for articles and abstracts. There was no limit to the time of publication of these articles.

RESULTS

In the TRA-PCI study by Becker *et al.,* (2009), a phase II trial, 573 patients with ACS (acute coronary syndrome) who underwent PCI were randomised to vorapaxar (loading dose 10, 20 or 40 mg) or placebo in addition to aspirin and clopidogrel. At 60 days, maintenance doses of 0.5, 1 or 2.5 mg per day were continued. It was not associated with an increase in Thrombolysis In Myocardial Infarction (TIMI) major plus minor bleeding versus placebo.

In a multinational phase III clinical trial conducted by Tricoci *et al.,* (2012), vorapaxar and placebo were given to the patients with acute coronary syndromes without ST-segment elevation. The primary end point was death due to cardiovascular causes like myocardial infarction, stroke, etc. In vorapaxar group, the primary end point occurred in 1031 of 6473 patients compared to 1102 of 6471 patients in the placebo group, leading to the early termination of trial, citing the safety reasons. Also the rate of mild to moderate bleeding was 7.2% in the vorapaxar group and 5.2% in the placebo. The intracranial bleeding was again higher with the vorapaxar group, 1.1% compared to 0.2% in placebo.

Morrow *et al.,* (2012) did another phase 3 trial of vorapaxar in the secondary prevention of atherothrombotic events. It was done on the patient population with a history of prior myocardial infarction, stroke etc. Half of the patients received vorapaxar (2.5 mg daily) and the other half received placebo and both the groups were followed up for a median of 30 months. The primary end point determining efficacy was the death due to myocardial infarction, or stroke etc. However, the study had to be terminated after 2 years in the patients with a history of prior stroke because of the high associated risk of intracranial hemorrhage. At 3 years, the primary end point had occurred in 9.3% patients in the vorapaxar group and in 10.5% patients in the placebo group. Moderate or severe bleeding occurred in 4.2% of patients who received vorapaxar and 2.5% of those who received placebo. Vorapaxar reduced the risk of cardiovascular death or ischemic events in patients with stable atherosclerosis but with an associated high bleeding risk, including intracranial hemorrhage.

Shinohara *et al.,* (2012), however got positive results for vorapaxar, in a study to assess the safety of the vorapaxar in Japanese patients with a history of ischemic stroke. 90 patients with previous ischemic stroke were randomized and given vorapaxar (1 or 2.5 mg) or placebo once daily for 60 days. All patients received aspirin (75-150 mg/day). The primary endpoint was overall incidence of adverse events during the protocol-defined treatment phase. Addition of vorapaxar to aspirin did not significantly increase the overall incidence of adverse events, including serious adverse events. None of the patients on vorapaxar plus aspirin experienced TIMI major or minor bleeding versus 1 patient treated with placebo. Nonfatal stroke occurred in 1 patient allocated to placebo and 1 patient allocated to vorapaxar. Therefore concluding that vorapaxar used in combination with aspirin was safe and well tolerated in Japanese subjects with a history of ischemic stroke

In TRA 2°P-TIMI 50 randomised, placebo-controlled, parallel trial, Scirica *et al.,* (2012) randomly assigned patients with a history of athero thrombosis to receive vorapaxar (2·5 mg daily) or matching placebo in a 1:1 ratio. Patients with a qualifying myocardial infarction within the previous 2 weeks to 12 months were analysed as a pre-defined subgroup. The primary efficacy endpoint was cardiovascular death, myocardial infarction, or stroke, analysed by intention to treat. Median follow-up was 2·5 years. Cardiovascular death, myocardial infarction, or stroke occurred in 610 of 8898 patients in the vorapaxar group and 750 of 8881 in the placebo group (8·1%vs 9·7%).

Table 1: Various studies done on vorapaxar

Study	Phase of the trial	Drugs used	Primary end point	Associated risks if any	Conclusions
TRA-PCI (Becker *et al.*, 2009)	II	vorapaxar vs placebo, with aspirin & clopido- grel	Clinically significant major or minor bleeding according to the TIMI scale	No	Well tolerated, No incidence of major or minor TIMI
TRACER (Tricoci *et al.*, 2012)	III	Vorapaxar vs placebo	Composite of death from cardiovascular causes, MI, stroke, etc.	Rates of moderate and severe bleeding were 7.2% in the vorapaxar c.f. 5.2% in the placebo group Intracranial hemorrhage rates were 1.1% with vorapaxar and 0.2% in placebo	Primary end point not significantly decreased with vorapaxar Added risk of bleeding with vorapaxar
TRA 2P–TIMI 50 (Morrow *et al.*, 2012)	III	-do-	-do-	Moderate or severe bleeding occurred in 4.2% in vorapaxar group and 2.5% in placebo group. Intracranial hemorrhage in the vorapaxar group was 1.0%, vs. 0.5% in the placebo group	vorapaxar reduced the primary end point in patients with stable atherosclerosis who were receiving standard therapy. Increased risk of moderate or severe bleeding, including intracranial hemorrhage
Subgroup analysis of TRA 2P–TIMI 50 (Scirica BM *et al.*, 2012)	III	-do-	-do-	Moderate or severe bleeding was 3·4%, in the vorapaxar group versus 2·1%, in the placebo group. Intracranial haemorrhage occurred in 0·6%, with vorapaxar versus 0·4%, with placebo	For patients with a history of myocardial infarction, vorapaxar reduces primary end point and increases the risk of moderate or severe bleeding.
Shinohara *et al.*, 2012	III	Vorapaxar vs placebo in addition to aspirin	Overall incidence of adverse events during the treatment phase	No	Vorapaxar did not significantly increase the overall incidence of adverse events Safe and well tolerated

Moderate or severe bleeding was more common in the vorapaxar group versus the placebo group (3·4% vs 2·1% Intracranial haemorrhage occurred in 0·6% patients with vorapaxar versus 0·4% with placebo. It was seen that for patients with a history of myocardial infarction, vorapaxar reduced the risk of cardiovascular death / ischaemic events when added to standard antiplatelet treatment, including aspirin, and increases the risk of moderate or severe bleeding. However there was no increase in the intracranial bleeding in the vorapaxar group.

The in-vitro effects of E5555 (atopaxar on platelet biomarkers in healthy volunteers and patients with coronary artery disease was studied by Serebruany *et al.,* (2009), and atopaxar was shown to completely inhibit thrombin induced platelet aggregation, along with some inhibitory effect on ADP and collagen induced aggregation of platelets. They proposed that atopaxar might enhance the antiplatelet action when given with aspirin and clopidogrel, pointing towards their possible synergistic use in patients requiring antiplatelet therapy.

A Double-blind, placebo-controlled Phase II trial of the E5555 (atopaxar) was done in Japanese patients with ACS or high-risk coronary artery disease by Goto *et al.,* (2010), and it was seen that E5555 (50, 100, and 200 mg) did not increase clinically significant bleeding and achieved a significant level of platelet inhibition. There was however, a significant dose-dependent increase in liver function abnormalities and QTc interval.

In another phase II trial with 603 subjects, by O'Donoghue *et al.,* (2011), primary objective was to evaluate the safety and tolerability of atopaxar in patients with ACS. The patients were already on clopidogrel and the incidence of bleeding was much higher in the atopaxar group as compared to the placebo group (1.8% versus 0%; P=0.12). There was not much difference in the incidence of cardiovascular death, myocardial infarction, stroke etc. in both atopaxar and placebo groups (8.03% versus 7.75%). However, with the highest dose group of atopaxar, rise in transaminases along with the QTc prolongation was seen. Keeping this unforeseen development in mind, it was proposed that more trials should be done to fully establish the efficacy and safety of atopaxar. But after these studies of atopaxar, indicating the liver damage, the further development of atopaxar was suspended (Huan Cui *et al.,* 2012) (Table 1).

DISCUSSION

Based on the phase II trial of vorapaxar (Becker *et al.,*2009), it was clear that vorapaxar, with its novel mechanism of action of thrombin receptor inhibition, holds promise for the antithrombotic effect in patients with prior MI, Ischemic stroke etc. In phase II trials for vorapaxar, the bleeding risk was same as that seen with placebo. However, phase III trial for vorapaxar has a different story to tell (Tricoci *et al.,* 2012), with significantly higher bleeding risk compared to placebo. It also demonstrated an increased incidence of intracranial bleeding in the patient on vorapaxar. This finding has disturbed the risk benefit balance for vorapaxar. However when a subgroup analysis was done for another phase III trial of vorapaxar (Morrow *et al.,* 2012) it was seen that vorapaxar offered benefit, if it was given in patients with no prior history of stroke or the subgroup of patients with no increased risk towards stroke. Hence, based on this subgroup analysis it might be said that vorapaxar might prove useful novel antiplatelet agent in a carefully selected patients population, keeping in mind the risk of intracranial bleeding involved in the patients who had a history of Transient Ischemic Attack (TIA) and stroke. In another carefully chosen patient population without the stroke history, vorapaxar displayed beneficial outcomes (Scirica *et al.,* 2012).

The study results of atopaxar however had a lower benefit compared to the risks involved, and thereby further research and development of atopaxar is needed to ensure its safety when used in humans.

Vorapaxar, as a specific competitive PAR 1 inhibitor, offers additional benefits in the patients needing the antiplatelet therapy and has to be used in carefully selected population of patients' in order to avoid the intracranial bleeding risk. Merck stated that it is planning to file for FDA and European approvals for

vorapaxar in 2013 as an indication for the prevention of cardiovascular events in patients with a history of heart attack (MI) and no history of TIA or stroke (Huan Cui *et al.,* 2012).

Conclusion

The inhibition of PAR 1 receptors by this novel class of drugs, does offer a bright and novel mechanism to provide additional benefits to the patients receiving antiplatelet drugs. However, the future success of any drug, builds on the improvements it has to offer in the terms of efficacy and side effects compared to the previous generation of drugs. The journey to develop a successful thrombin receptor antagonist will undoubtedly be full of challenges, as demonstrated by the clinical trials of vorapaxar and atopaxar (Huan Cui *et al.*, 2012). The need of the hour is to properly balance the efficacy and safety, with regards to the bleeding profile of the thrombin receptor antagonist. There is a large unmet medical need and a potentially huge commercial market. With the ongoing research in this field, hopefully newer generations of thrombin receptor antagonists that have a better risk benefit profile will success-fully make it to the market. Till then Vorapaxar holds a huge promise, with a carefully selected population of patients.

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