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Vorapaxar, a Protease-Activated Receptor-1 Antagonist, a Double –Edged Sword!

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Abstract: Acute coronary syndrome (ACS) constitutes a group of pathophysiological entities resulting from reduced blood flow in the coronary arteries leading to decreased or improper functioning or death of heart muscle. Such patients are usually prescribed combination antiplatelet drug therapy, containing acetylsalicylic acid (aspirin) and an adenosine diphosphate receptor inhibitor to prevent recurrence of ischemic events. The combination prophylactic therapy to certain extend has been successful in preventing secondary complications including ischemic/thrombotic events in these patients. However, research is still on for newer advances in anti-thrombotic therapy that can further prevent secondary complications of Acute Coronary Syndrome.

Vorapaxar is a newer drug recommended along with aspirin or clopidogril for prevention of recurrence of cardiac events. Vorapaxar, a thrombin receptor antagonist acts by reversible inhibition of the protease-activated receptor-1 (PAR-1). PAR-1 is expressed on platelets, and it inhibits platelet aggregation, both thrombin-induced and thrombin receptor agonist peptide (TRAP)-induced. Various trials world -wide have documented its efficacy as an anti-platelet agent for preventing recurrent cardiovascular ischemic events but at the expense of increased bleeding complications including intracranial haemorrhage (ICH), when compared to standard therapy alone. For the same reason, vorapaxar is contraindicated in patients with prior stroke, transient ischemic attack and ICH.

U.S. Food and Drug Administration (FDA) approved vorapaxar in May 2014 as an antiplatelet agent along with standard anti-platelet therapy for the reduction of recurring thrombotic cardiovascular events in patients with a history of myocardial infarction or with peripheral arterial disease. Vorapaxar is developed and marketed by Merck Sharp Dohme and is available by the brand name '**Zontivity'** as 2.5 mg oral tablet equivalent to 2.08 mg of vorapaxar sulfate.. There are two patents protecting this drug.

Keywords: Anti platelet therapy, PAR-1 antagonist, acute coronary syndrome, myocardial Infarction, peripheral arterial disease, vorapaxar.

INTRODUCTION

Acute coronary syndrome (ACS) is the leading cause of cardiovascular mortality and morbidity; it is usually managed with invasive and non-invasive medical treatment modalities. Platelets play an essential role in the pathogenesis of thrombus formation and have been the target of various pharmacotherapies [1]. The combination of acetylsalicylic acid (ASA) and thienopyridine (clopidogrel, prasugrel) or Triazolopyrimidine (Ticagrelor) has shown definite improvement in terms of recurring rate of thrombus formation but each has shown superiority over the other in ACS in separate studies. Ticagrelor and prasugrel were found to be superior over clopidogrel for the treatment of ACS in PLATO and TRITON-TIMI-38 trials [2-4] whereas in TRILOGY-ACS trial, clopidogrel was at par with ticagrelor and prasugrel [4, 5]. Current guidelines of the American Heart association and the European Society of Cardiology recommend the use of dual antiplatelet therapy aspirin/ticagrelor in the acute phase, even in patients pre treated with clopidogrel. The guidelines limit the use of prasugrel to P2Y12 inhibitor naïve patients in whom PCI is indicated, unless there is high risk of life threatening bleeding [6, 7]. The prescribed treatment is to be continued for 12 months in patients of non-ST-elevation ACS. However, despite these advances in the treatment strategies, the 12 month risk of recurrent ischemia still remains as high as 10% among these patients [8, 9]. This fact has prompted researchers to explore and investigate newer anti-platelet drugs; recent addition to the list is a protease-activated receptor-1 (PAR-1) antagonist, vorapaxar. Vorapaxar inhibits thrombin- induced and thrombin receptor agonist peptide (TRAP)-induced platelet activation and consequent aggregation [10, 11]. The current review focusses on the pharmacodynamics and pharmacokinetics of this drug, including its therapeutic benefits and associated side effects.

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1. CHEMICAL CHARACTERISTICS OF VORAPAXAR

Vorapaxar is synthetic tricyclic phenylpyridine analogue of himbacine [12, 13]. The chemical name of the active substance Vorapaxar sulphate is Ethyl [[1R,3aR,4aR,6R,8aR, 9S,9aS)-9-{[E)-2-[5-[3-fluorophenyl)-2-pyridinyl)vinyl}-1-methyl-3-oxododecahydronaphtho[2,3-c)furan-6-yl)carbamate sulphate, corresponding to the molecular formula $C_{29}H_{33}FN_2O_4.H_2SO_4$. It is white to off-white, crystalline powder, slightly hygroscopic and sparingly soluble in ethanol and insoluble in aqueous solution at pH >3.0 [14].

2. DEVELOPMENTAL MILESTONES

2.1. Phase I Trial

Various phase I studies by Kosoglou and group proved the effectiveness of vorapaxar in inhibiting thrombin receptor-agonist peptide (TRAP)-induced platelet aggregation. These trials also investigated the safety, pharmacokinetics or pharmacodynamics of vorapaxar in different populations [15, 16]. These conclusions motivated other investigations to use vorapaxar in the clinical settings.

2.2. Phase II Trials

TRA-PCI trial by Becker and colleagues [17]

In this international multicentric trial, patients >45 years of age undergoing non-urgent Percutaneous Coronary Intervention (PCI) or coronary angiography with planned PCI were randomly kept on oral loading dose of 10 mg, 20 mg, or 40 mg or matching placebo in a 3:1 ratio of SCH 530348 (vorapaxar). The test group i.e the group taking SCH 530348 who in the due course underwent PCI (primary PCI cohort) continued receiving an oral maintenance dose (0·5 mg, 1·0 mg, or 2·5 mg per day), and the patients in the placebo group were maintained on placebo for 60 days. The primary endpoint was the manifestation of clinically significant major or minor bleeding according to the thrombolysis in myocardial infarction (TIMI) scale. It was a double blinded trial in which both investigators and patients were not aware of treatment allocation. There was a non-significant difference in the occurrence of the primary endpoint at all the doses (loading as well as maintenance doses) of SCH 530348 in comparison to the placebo group. 257 patients were assigned to placebo and 773 to SCH 530348. The primary endpoint occurred in 2 (2%) of 129, 3 (3%) of 120, and 7 (4%) of 173 patients, respectively, in the SCH 530348 10 mg, 20 mg, and 40 mg groups compared with 5 (3%) of 151 patients in the placebo group (p=0.5786). TIMI major plus minor bleeding occurred in 3 (2%) of 136, 5 (4%) of 139, and 4 (3%) of 138 patients given SCH 530348 0.5 mg, 1.0 mg, and 2.5 mg once per day, respectively (p=0.7561). It was interpreted that SCH 530348 was tolerated quite well orally and did not cause increased TIMI bleeding, even when administered concomitantly with aspirin and clopidogrel.

Trial by Goto *et al.* [18]:

In this multicentre, randomized, double-blind, placebo controlled trial, the safety of vorapaxar (SCH530348) in Japanese patients with NSTE ACS was evaluated. Patients with planned PCI received standard-of-care (aspirin, ticlopidine, and heparin) and were randomized to receive either SCH530348 (20 or 40 mg loading dose followed by 1 mg/d or 2.5 mg/d maintenance dose for 60 days) or placebo. The key safety endpoint and exploratory efficacy endpoint was TIMI major and minor bleeding and MACE (major adverse cardiac events)/death within 60 days respectively in the primary cohort. It was observed that SCH530348 added to standard treatment did not significantly increase the rate of bleeding complications in the PCI cohort and was concluded that vorapaxar added to standard-of-care is safe in Japanese subjects with NSTE ACS but also significantly reduces the incidence of peri-procedural MI in subjects undergoing urgent PCI (16.9% vs 42.9% respectively; p=0.013).

Shinohara *et al.* trial [19]:

Another phase 2 clinical trial was conducted in Japanese population by Shinohara and colleagues. It was a multicentre, randomized, double-blind, placebo controlled trial in which patients who had ischemic stroke 14 days to 1 year before selection were included. The patients were randomized to receive vorapaxar in the dose of 1 or 2.5 mg or placebo once daily for 60 days along with low dose aspirin. The primary endpoint was overall incidence of adverse events during the protocol-defined treatment phase (60 days). Addition of vorapaxar to aspirin did not significantly increase the overall incidence of mild as well as serious adverse events. None of the patients treated with vorapaxar plus aspirin experienced TIMI major or minor bleeding, though one patient treated with placebo had bleeding. Nonfatal stroke occurred in one patient in the placebo group and one patient in the vorapaxar treatment group. It was concluded that vorapaxar along with standard doses of aspirin is well tolerated and could be used safely Japanese subjects with a history of ischemic stroke.

2.3. Phase III Trials

Merck and Co. conducted two large scale multinational phase III clinical trials for vorapaxar for the treatment and prevention of recurrent cardiac complications in patients with ACS with history of MI or stroke; and also in patients with ASC and those with Peripheral arterial Disease (PAD).

Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome trial (TRA.CER) [20-24].

In this multinational, double-blind, randomized trial, vorapaxar was compared with placebo in patients who had acute coronary syndromes without ST-segment elevation. The primary end point constituted death from any cardiovascular causes, myocardial infarction or stroke and recurrent ischemia requiring rehospitalisation, or urgent coronary revascularization. The primary end point occurred in 18.5% patients receiving vorapaxar versus 19.9% patients receiving placebo at the end of the follow-up phase (hazard ratio [HR], 0.92; 95% confidence interval[CI], 0.85-1.01; p=0.07). Death from cardiovascular causes, myocardial infarction, or stroke occurred in 14.7% patients in the vorapaxar group versus 16.4% in the placebo group (HR, 0.89, 95% CI, 0.81-0.98; p=0.02). Incidence of moderate and severe bleeding was increased in the vorapaxar group. Intracranial haemorrhage occurred in 1.1% and 0.2% in the vorapaxar and placebo group respectively (HR, 3.39; 95% CI, 1.78-6.45;

p<0.001). Adverse events, other than bleeding were also more in the vorapaxar group than the placebo group, the rates were 1.1% and 0.2% respectively. It was concluded from the study that in patients with acute coronary syndromes, the addition of vorapaxar to standard therapy was not of much benefit in terms of the reduction in the primary composite end point but also associated with a significantly increased risk of major bleeding, including intracranial haemorrhage. During the trail, the drug and safety board recommended that vorapaxar should be discontinued in patients with history of stroke, since protocol defined number of primary efficacy end point had been reached. Following this, the trail was terminated. However subgroup analysis from TRA.CER trail showed that in NSTE ACS patients undergoing Coronary Artery Bypass Graft surgery (CABG), vorapaxar was associated with a significant reduction in ischemic events (8.2% vs 12.9% in the vorapaxar and placebo group respectively; HR 0.55; 95% CI 0.36-0.86; p=0.125) without significant increase in major CABG-related bleeding (9.7% vs 7.3% in the vorapaxar and placebo group respectively; HR 1.36; 95% CI 0.92-2.02; p=0.005) [22]. Another sub group analysis by Leonardi *et al* interpreted that vorapaxar use is associated with a reduction of MI, including total number of infarcts. The reduced incidence was more evident in type 1 MI and continued over time (HR, 0.83; 95% CI, 0.73-0.95; P = 0.007) [24].

Thrombin Receptor Antagonist *in* Secondary Prevention of Atherothrombotic Ischemic Events Thrombolysis in Myocardial Infarction (TRA 2^0P TIMI 50) trial [25-30]:

TRA 2^0P TIMI 50 trial was a multinational, double-blinded, placebo-controlled randomized trial in which efficacy and safety of vorapaxar was tested in patients with history of MI and PAD. At 3 years, the endpoint of CV death, MI, or stroke was significantly reduced with vorapaxar (7.9%) compared with placebo (9.5%) (HR, 0.80; 95% CI, 0.73-0.89; p<0.001). Vorapaxar also significantly reduced the composite of CV death, MI, stroke, and urgent coronary revascularization (p<0.001), as well as the rate of CV death or MI (p<0.001). The study concluded that in patients with prior MI or PAD without history of stroke or TIA, vorapaxar when added to standard therapy is effective in preventing long-term secondary thrombotic CV events, while increasing moderate or severe bleeding [27]. A sub group analysis also documented that vorapaxar reduces ischemic stroke in patients with MI or PAD without significant increase in the risk of haemorrhagic conversion or death in patients who experienced a first ischemic stroke on vorapaxar. Even though, the incidence of primary haemorrhagic stroke was increased (0.6% in vorapaxar vs 0.5% in placebo; HR, 1.46; 95% CI 0.92-2.31; p=0.10), vorapaxar reduced the overall occurrence of stroke [27]. Although the risk of cardiovascular death, myocardial infarction, or stroke in patients with peripheral artery disease was not reduced by vorapaxar; but, it significantly reduced acute limb ischemia (2.3% versus 3.9%; hazard ratio, 0.58; 95% confidence interval, 0.39-0.86; P=0.006) and peripheral revascularization in these patients (18.4% versus 22.2%; hazard ratio, 0.84; 95% confidence interval, 0.73-0.97; P=0.017) [31].

3. CLINICAL PHARMACOLOGY

3.1. Mechanism of Action

Vorapaxar is a reversible antagonist of protease-activated receptor-1 expressed on human platelets; but due to its long half-life, it is effectively irreversible. PAR-1 mediates platelet activation at low concentration of thrombin [32]. Vorapaxar does not have inhibitory effect on ADP, thromboxane mimetic or collagen induced platelet aggregation. It has no effect on coagulation parameters *in vitro*.

3.2. Pharmacokinetics and Pharmacodynamics

Vorapaxar is orally active ingredient of PAR-1 with complete oral bio availability. At recommended dose, it achieves >80% inhibition of thrombin-induced platelet aggregation. Duration of inhibition is dose and concentration dependent [16, 20]. Vorapaxar administration does not require consideration of meal or antacid use [10, 20]. Vorapaxar and its active metabolite M_{20} remain in the circulation bound to plasma proteins [15, 20]. Both have shown not to cause clinically significant inhibition or induction of major CYP isoforms [16, 33]. No dose adjustments is required when used along with digoxin, rosiglitazone or prasugral. Concomitant use with warfarin should be avoided [34]. Vorapaxar can cross placental barrier and can act on developing foetuses. It is also secreted in the milk of lactating female rats, exposing nursing pups to its effects [33]. It undergoes metabolism in the liver by cytochrome P450 and is eliminated in the faeces and partly in the urine [20].

3.3. Toxicity of Vorapaxar

In animals, studies of vorapaxar did not reveal any major adverse effects. In cynomolgus monkeys, 1 mg/kg of vorapaxar did not increase post-surgical blood loss, when administered alone or in combination with aspirin and clopidogrel [35]. No carcinogenic, mutagenic or phototoxic potential was associated with vorapaxar use even at a much higher systemic exposure. Fertility is not affected by its use [36]. Mixed adverse drug reactions were observed in dose ranging studies and included headache, upper respiratory infection and fatigue. None of the ADRs were dose-related [33].

Phase II study by Becker and group did not report increased bleeding in patients receiving 40 mg loading dose of vorapaxar, followed by 2.5 mg maintenance dose [17]. However, the two major phase III clinical trials designed to test the efficacy and safety of vorapaxar revealed increased bleeding as the major complication of the treatment. During these trails, bleeding was assessed using Global Utilization of Streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO) and TIMI classification [37]. The safety end point was kept as GUSTO moderate to severe bleeding [21, 27, 30]. During TRA.CER trial, adding vorapaxar to the standard therapy was found not to significantly reduce the composite end point but was found to significantly increase the risk of bleeding including intracranial haemorrhage. Rate of GUSTO moderate to severe bleeding as well as rate of clinically significant TIMI bleeding was increased among patients on vorapaxar. These findings prompted safety monitoring board to order termination of this study medication in patients with a history of stroke [22,

28]. The increased bleeding was also seen in patients with history of TIA without prior known stroke [28]. However, in TRA 2^0P TIMI trial, inhibition of PAR-1 reduced the risk of ischemia in patients with stable atherosclerosis without history of stroke. The risk of bleeding was still present but in these patients the net clinical outcome over weighted the bleeding complication with the use of vorapaxar. More so, without history of stroke the incidence of intracranial haemorrhage was not significantly increased in the vorapaxar group [30]. Owing to the increased intracranial bleeding associated with its use in patients with history of stroke, TIA or ICH, the drug is contra indicated in such patients.

4. CURRENT AND FUTURE DEVELOPMENTS

Merck Sharp Dohme has obtained two patents related to vorapaxar.

(1) Patent number US 7, 235,567; titled "Crystalline polymorph of a bisulphate salt of a thrombin-receptor antagonist". Inventor is Wu Wenxue (Princeton Junction, NJ). Assignee is Schering Corporation (Kenilworth, NJ). The patent will expire on Jun 13, 2021 [38, 39].

(2) Patent number 7,304,078 titled "Thrombin receptor antagonist", Inventors are Chackalamannil S (Califon, NJ), Greenlee WJ (Teaneck, NJ), Wang Y (North Brunswick) Wu W (Princeton Junction, NJ), Veltri EP (Princeton, NJ), Xia Y (Edison, NJ). Assignee is Schering Corporation (Kenilworth, NJ). The patent expires on Apr 6, 2024 [38, 40].

The drug "ZONTIVITY" with active ingredient vorapaxar was approved by US Food and Drug Administration on May 8, 2014 for reduction of atherothrombotic events in patients with a history of MI and PDA without a history of stroke and TIA. The drug is marketed by Merck Sharp Dohme and is available as 2.5mg oral tablet (equivalent to 2.08mg of vorapaxar).

Dual antiplatelet therapy always carries increased risk of bleeding, vorapaxar along with standard therapy is no exception. Usefulness of combination anti platelet therapy is determined by its benefits weighted against the associated risk. Vorapaxar was found to have a beneficial clinical outcome in patients with ACS and PDA without history of stroke and TIA, when weighted against the risk of severe bleeding. It could be concluded that the most important aspect while considering vorapaxar combination therapy is the appropriate selection of patients. Vorapaxar has proved to be effective along with aspirin or clopidogrel in reducing the risk of cardiovascular death, MI and stroke (recurrent events) in patients with ACS (especially with history of MI). On the contrary, it also increases moderate to severe bleeding risk, including intracranial haemorrhage in patients with history of stroke; hence, vorapaxar is contraindicated in patients of stroke and TIA.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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