Vorapaxar: Targeting a Novel Antiplatelet Pathway
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INTRODUCTION

In the setting of non–ST-segment elevation acute coronary syndromes (NSTE ACS), optimal management includes multitiered antithrombotic therapy. Acute and postcardiac-event antithrombotic management is focused on the central role platelets play in thrombosis. Platelets can be activated by a number of different agonists, including thromboxane A2 (TXA2), adenosine diphosphate (ADP), epinephrine, collagen, and thrombin.1,2

Aspirin irreversibly inhibits cyclooxygenase-1 (COX-1) and impedes the formation of TXA2, leading to a decrease in platelet activation and aggregation.1 Clopidogrel event irreversibly inhibits the P2Y12 ADP receptor, also leading to decreased platelet activation and aggregation.3 The concurrent blockade of multiple platelet-aggregating pathways has been shown to reduce ischemic cardiovascular events compared with aspirin alone in various cardiovascular conditions,2 and yet there is an increase in bleeding with dual antiplatelet therapy.

Therefore, novel pathways to reduce platelet-mediated thrombosis without increasing bleeding liability are clinically warranted.4,5

Inhibition of thrombin-mediated platelet activation may provide an alternate pathway for antithrombotic management with a better safety profile. Thrombin is a potent platelet activator through proteolytic activation of cell-surface protease-activated receptors (PARs). Four PARs have been identified: PAR-1, -2, -3, and -4. PAR-1, also known as the thrombin receptor, is widely expressed in human platelets.2,4–7

The PAR-1 receptor has gained interest since PAR-1 blockade may produce potent antiplatelet effects without affecting the ability of thrombin to generate fibrin and without inhibiting platelet activation by collagen.2,4–6 Theoretically, this alternate pathway would block platelet activation during clot formation while preserving essential vascular repair and protective hemostatic function.2,4–7 The PAR-1 receptor is also of interest because of its role in the vascular repair process in atherosclerotic plaques and in the restenosis that often occurs after percutaneous coronary intervention (PCI).8 Currently in phase 3 trials, vorapaxar (SCH 530348, Schering) may provide an alternative option in antiplatelet therapy.

PHARMACOLOGY AND MECHANISM OF ACTION

A synthetic analog of the natural product himbacine,5,6,8 vorapaxar (Figure 1) is a novel, orally active, non-protein, highly selective, competitive PAR-1 inhibitor.2,4–7,9 Vorapaxar is a thrombin receptor antagonist (TRA) that exhibits reversible inhibition (Table 1). It inhibits thrombin receptor-activating peptide (TRAP)–induced platelet aggregation in a dose-dependent manner.2,5 In preclinical studies, vorapaxar did not affect the platelet aggregation induced by ADP, TXA2, or collagen, nor did it affect prothrombin time or activated partial thromboplastin time.7

PHARMACOKINETICS AND PHARMACODYNAMICS

An orally administered medication, vorapaxar is rapidly and almost completely absorbed via the gastrointestinal tract. Peak antiplatelet effects are seen within one to two hours after an oral loading dose.2,5,10–12 A clinically insignificant delay in absorption and increase in exposure were observed with the administration of food. Moreover, administration of an antacid yielded a clinically insignificant decrease in exposure and in the maximal serum concentration. Therefore, vorapaxar can be administered without consideration of meals or antacid use.2,5,13

Vorapaxar is metabolized mainly by the cytochrome P450 (CYP) 3A4 enzyme. The major route of elimination is the feces, with minor renal excretion (less than 5% of the dose).2 Vorapaxar is slowly eliminated and has a half-life of 159 to 311 hours.2,11

Figure 1 Chemical structure of vorapaxar.
(From the National Center for Biotechnology Information, National Institutes of Health.)

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pharmacokinetics and pharmacodynamics were not observed in Japanese and Caucasian subjects.14 There is no known antidote for vorapaxar overdose.5

**CLINICAL EFFICACY**

**Phase 2 Studies**

**Becker: TRA–PCI Trial15**

Becker and colleagues conducted an international, multicenter, randomized, double-blind study to assess the safety and tolerability of vorapaxar in 1,030 patients undergoing non-urgent PCI or coronary angiography with planned PCI. The patients were assigned to one of four loading doses: vorapaxar 10 mg (n = 222), vorapaxar 20 mg (n = 238), vorapaxar 40 mg (n = 313), or matching placebo (n = 257). Before receiving a loading dose, all patients were given a dose of aspirin orally (162–325 mg) or intravenously (150–500 mg).

Patients were enrolled in the study if they were 45 years of age or older, had symptoms of coronary artery disease (CAD), and were scheduled to undergo non-urgent PCI or non-urgent coronary angiography with planned PCI.

Of the 1,030 patients randomly assigned to treatment, 573 underwent PCI and were included in the primary PCI cohort (n = 129 for vorapaxar 10 mg; n = 120 for vorapaxar 20 mg; n = 175 for vorapaxar 40 mg; and n = 151 for placebo). All patients in the primary PCI cohort received unfractionated heparin, low-molecular-weight heparin, or bivalirudin, followed by a loading dose of clopidogrel (300 to 600 mg). A daily maintenance dose of vorapaxar 0.5 mg (n = 136), vorapaxar 1.0 mg (n = 139), or vorapaxor 2.5 mg (n = 138) was continued for 60 days after PCI in the primary cohort, and patients were scheduled for return visits 30 days and 60 days after enrollment. A placebo maintenance dose was given to patients who had received a placebo loading dose of vorapaxar (n = 149). Eleven patients in the primary cohort discontinued the study before receiving a maintenance dose (reasons unknown). No maintenance dose was given to patients who did not undergo PCI (secondary non-PCI cohort; n = 457); however, these patients underwent coronary artery bypass grafting (CABG) (n = 76) or were managed medically (n = 381) and were followed for the remainder of the study.

The primary endpoint was the incidence of major or minor bleeding during treatment in the primary PCI cohort, as determined by Thrombolysis in Myocardial Infarction (TIMI) criteria. Secondary endpoints included overt and clinically important bleeding not meeting TIMI criteria for major or minor bleeding; measures of inhibition of platelet aggregation; and cardiovascular outcomes, including death, non-fatal myocardial infarction (MI), and stroke. The primary and secondary endpoints in the secondary non-PCI cohort were TIMI major or minor bleeding, quantitative chest-tube drainage, the need for transfusion of blood products, and the need for surgical re-exploration in patients undergoing surgical revascularization.

In the primary PCI cohort, the incidence of TIMI major or minor bleeding (the primary endpoint) was similar in those receiving vorapaxar 10 mg (2/129; 2%), 20 mg (3/120; 3%) or 40 mg (7/173; 4%) compared with patients receiving placebo (5/151; 3%) (P = 0.5786). Further, no differences in TIMI major or minor bleeding (P = 0.7713) or non-TIMI bleeding (P = 0.065) were noted when all placebo groups and all vorapaxor groups (loading and maintenance doses) were compared. The highest dose combination tested—a 40-mg loading dose of vorapaxor followed by a maintenance dose of 2.5 mg daily—was not linked to TIMI major bleeding, but TIMI minor bleeding was observed in two patients (2/58; 3%).

No significant differences were observed in death, non-fatal MI, or stroke when placebo was compared with vorapaxor (all doses) given as either a loading dose (absolute risk difference, –2.5%; range, –7.2% to +2.1%) or a maintenance dose (absolute risk difference, –2.8%; range, –11.5% to +6.0%).

**Platelet aggregation, defined as at least 80% inhibition of TRAP, was observed in 42.9% of patients within 120 minutes after receiving the lowest loading dose of vorapaxor (10 mg) and in 96.3% of patients within 120 minutes after receiving the highest loading dose (40 mg). At 30 and 60 days of maintenance therapy, at least 80% of TRAP-induced platelet aggregation was seen in 90.9% of patients receiving vorapaxor 0.5 mg daily and in 100% of patients receiving vorapaxor 1.0 or 2.5 mg daily.**

In the secondary non-PCI cohort, no significant differences in TIMI major or minor bleeding were noted between placebo and vorapaxor (all doses) in both subgroups: patients undergoing CABG (79% vs. 90%, respectively; absolute difference in rate: +11.2%; range: –6.9% to +29.3%) or patients being medically managed (0% vs. 1%, respectively; absolute difference in rate, +1%; range, –0.2% to +2.1%).

The authors concluded that treatment with vorapaxor was well tolerated and did not result in an increased incidence of TIMI bleeding among patients with CAD undergoing PCI and concomitantly receiving aspirin and clopidogrel.

**Goto et al.4**

Goto and associates conducted a multicenter, randomized, double-blind, placebo-controlled, sequential, parallel-group trial in Japan to assess the safety and efficacy of vorapaxor in patients with NSTE ACS who were receiving standard-of-care therapy with planned PCI. The study included men and women 18 years of age and older with a history of ischemic chest discomfort of at least 10 minutes in duration within 24 hours before enrollment. Patients were excluded if they were pregnant, had a serious illness, or...
used an investigational drug within 30 days before study entry. Patients were also excluded if they had a history of bleeding diathesis, severe hypertension, or major surgery within 2 weeks before study entry; had a platelet count of less than 100,000/mm³; or had impaired renal or hepatic function.

A total of 117 patients were randomly assigned to receive a loading dose of vorapaxar 20 mg, vorapaxar 40 mg, or placebo not less than one hour before catheterization. A maintenance dose of vorapaxar 1.0 mg, vorapaxar 2.5 mg, or placebo was given for an additional 59 days to patients who initiated PCI (primary PCI cohort; n = 92). Patients who did not initiate PCI (n = 25) were classified as the secondary non-PCI cohort and were managed medically or underwent CABG. All patients were receiving standard-of-care therapy—aspirin, ticlopidine (Ticlid, Roche), and heparin—at the time of enrollment. The doses of these medications, however, were not stated in the published report.

The exploratory efficacy endpoints included all-cause death and major adverse cardiovascular events (MACE), which consisted of non-fatal MI, non-fatal stroke, hospitalization for recurrent ischemia, and urgent coronary revascularization. The key safety endpoint was TIMI major and minor bleeding in the PCI cohort. TIMI major bleeding was defined as intracranial hemorrhage or clinically significant overt signs of bleeding associated with a decrease in the hemoglobin concentration of more than 5 g/dL (or a decrease in hematocrit of more than 15%). TIMI minor bleeding was defined as clinically overt signs of bleeding (including bleeding detected via imaging) associated with a decrease in the hemoglobin concentration of between 3 and 5 g/dL (or a decrease in hematocrit of between 9% and 15%) that did not otherwise meet the criteria for major bleeding.

In the primary PCI cohort, the incidence of periprocedural MIs (one component of MACE) in patients receiving vorapaxar plus standard therapy was significantly lower compared with that in patients receiving placebo plus standard therapy (16.9% vs. 42.9% respectively, \( P = 0.013 \)). Additional MACE components (i.e., non-fatal stroke, recurrent ischemia with hospitalization, or urgent coronary revascularization) and death did not occur in the primary PCI cohort.

TIMI major and minor bleeding occurred in 14% of patients receiving vorapaxar and in 10% of patients receiving placebo (point estimate of the difference, 4.6%; 95% confidence interval [CI], –10.4 to +19.5). Clinically important bleeding, defined as the composite incidence of intracranial bleeding and bleeding requiring blood transfusion and rehospitalization, occurred in five patients (7%) receiving vorapaxar and in no patients receiving placebo. Discontinuation resulting from any adverse event (AE) was observed in 14 of 71 patients (20%) receiving vorapaxar and in 8 of 21 patients (38%) receiving placebo.

In the secondary non-PCI cohort, 23 of 25 patients received vorapaxar as a bolus; three of these patients (13%) experienced TIMI major bleeding.

The authors concluded that the addition of vorapaxar to standard therapy was associated with a significant reduction in the incidence of periprocedural MI without an increased risk of bleeding in Japanese patients with NSTEMI ACS.

Shinohara et al.\(^{16}\)

Shinohara and colleagues conducted a multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the safety of vorapaxar in Japanese patients with a history of ischemic cerebral infarction receiving aspirin. A total of 90 subjects received vorapaxar (1.0 mg or 2.5 mg) or placebo once daily for a total of 60 days. In addition to vorapaxar or placebo, all patients were given daily aspirin at doses ranging from 75 mg to 150 mg.

The study included patients 18 years of age or older with stable ischemic stroke that occurred between 14 days and one year before randomization with no neurological deficits for at least 24 hours. Patients were excluded if they had experienced a cardiogenic cerebral embolism, bleeding diatheses, or an abnormal bleeding episode within 30 days before study entry; a platelet count of below 100,000/mm³; or major surgery within 2 weeks before study entry. Patients were also excluded if they had systolic blood pressure (BP) exceeding 200 mm Hg or diastolic BP exceeding 110 mm Hg; a history of cerebral bleeding or evidence of bleeding on computed tomography (CT) or magnetic resonance imaging (MRI); liver enzyme elevations greater than two times the upper limit of normal (ULN); or renal dysfunction. Pregnant women and patients who were scheduled for carotid or coronary vascular interventions were also excluded from the study.

The primary endpoint was the overall incidence of any AE, excluding MACE. Secondary endpoints included bleeding, which was categorized as TIMI major bleeding, TIMI minor bleeding, or clinically important bleeding. Serious AEs were defined as any AE that caused any of the following: death; life-threatening, persistent, or significant disability or incapacity that required inpatient hospitalization or prolonged hospitalization; congenital anomalies or birth defects; a reduction in platelet count to less than 50,000/mm³; and other serious events. The exploratory efficacy endpoints included cardiovascular death and MACE.

The overall incidence of any non-MACE was similar between subjects receiving vorapaxar and placebo during the 60-day treatment phase (87% [54/62] vs. 79% [22/28], respectively; point estimate of the difference, 8.5%; 95% CI, –8.8% to +25.9%). No subjects in the vorapaxar group experienced TIMI major, TIMI minor, or clinically important bleeding, whereas one patient in the placebo group experienced TIMI minor bleeding (a decreased hematocrit level). The incidence of serious AEs was similar between the vorapaxar and placebo groups (3% [2/62] vs. 4% [1/28], respectively). Non-fatal ischemic stroke occurred in one patient in the vorapaxar group (1.0 mg) and in one patient in the placebo group.

The results of this study indicated that the addition of vorapaxar (1.0 mg or 2.5 mg) once daily to aspirin therapy in Japanese subjects with a history of ischemic stroke was not associated with an increased risk of bleeding or ischemic events.

**Phase 3 Studies**

**TRA 2P–TIMI 50 Trial (Study Design and Rationale)**\(^8,17\)

The Thrombin-Receptor Antagonist in the Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2P–TIMI 50 trial is an ongoing phase 3, randomized, mutinational, double-blind, placebo-controlled, study designed to evaluate the efficacy and safety of vora-
Vorapaxar as long-term therapy in patients with established atherosclerosis receiving standard treatment.

Patients were enrolled if they had a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems, as evidenced by (1) spontaneous (type 1) MI within two weeks to 12 months before enrollment, (2) ischemic (presumed thrombotic) stroke within two weeks to 12 months before enrollment, or (3) a history of intermittent claudication in conjunction with an ankle-brachial index of less than 0.85 or previous revascularization for limb ischemia. Patients with a history of bleeding diathesis, those receiving warfarin, and those with active hepatobiliary disease were excluded.

A total of 26,447 patients received either vorapaxar 2.5 mg or matching placebo once daily. Randomization was stratified by the type of disease: CAD, cerebrovascular disease (CVD), or peripheral vascular disease (PVD). Loading doses of vorapaxar were not given, because a rapid onset of effect was not required in this study’s setting of stable disease. All other drugs, including antiplatelet agents, were given at the discretion of the medical staff according to local treatment guidelines. Follow-up visits were scheduled at 30 days, 4 months, 8 months, 12 months, and every 6 months thereafter until completion of the study.

The primary endpoint is a composite of cardiovascular death, MI, stroke, recurrent ischemia with rehospitalization, and urgent coronary revascularization. The key secondary endpoint was a composite of cardiovascular death, MI, and stroke. Safety was assessed by a composite of moderate and severe GUSTO bleeding and clinically significant TIMI bleeding. TRACER was event-driven, and the investigators planned to continue the trial until 2,334 primary efficacy endpoints and 1,457 key secondary efficacy endpoints had been reached. An interim analysis was planned when approximately half of both the primary and key secondary efficacy endpoints had been recorded.

As in the TRACER trial, compared with placebo.

The Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRAÂ„CER) trial was a phase 3, prospective, randomized, double-blind, multicenter study designed to examine the role of vorapaxar in addition to standard care in the management of patients with high-risk NSTE ACS.

The study planned to enroll and randomly assign 10,000 patients to receive a 40-mg loading dose of vorapaxar or placebo. A daily maintenance dose of vorapaxar 2.5 mg or placebo was started the day after randomization and was planned to continue until the end of the study or for at least 1 year. Follow-up visits were scheduled at 30 days, 4 months, 8 months, 12 months, and every 6 months after the first year for the rest of the study.

Many safety outcomes, including bleeding by GUSTO and TIMI criteria, as well as ADRs and laboratory abnormalities. In press releases from earlier in the year, Merck announced termination of the TRACER study, with all patients discontinuing the use of vorapaxar. In addition, at the recommendation of the DSMB, patients who experienced a stroke before or after entry into the TRACER trial were immediately withdrawn from treatment with vorapaxar. Patients with a previous MI or PVD (approximately 75% of enrolled patients) continued to receive the study drug.

No other non-bleeding ADRs occurred more frequently in patients treated with vorapaxar, even at the highest doses studied, compared with placebo.

Drug Interactions

Given that vorapaxar is metabolized primarily by the CYP3A4 enzyme, coadministration of potent CYP3A4 inhibitors (e.g., ketoconazole) may increase the plasma concentration of vorapaxar. Coadministration of ketoconazole for 3 weeks increased vorapaxar exposure by twofold. Conversely, potent inducers (e.g., rifampin) may reduce plasma concentrations of vorapaxar. Coadministration of vorapaxar and rifampin for 3 weeks reduced vorapaxar exposure by 50%.
**Dosage and Administration**

Phase 1 dose-ranging studies of vorapaxar examined one-time loading doses of 5, 10, 20, and 40 mg and maintenance doses of 0.5, 1.0, and 2.5 mg daily, given in the morning. Even though both the 20- and 40-mg loading doses of vorapaxar produced greater than 80% platelet inhibition at one hour, the 40-mg dose did so in a higher number of patients. Only the 2.5-mg maintenance dose achieved more than 80% platelet inhibition at day 7. Further, the 40-mg loading dose, followed by a maintenance dose of 2.5 mg, was found to effectively inhibit platelets for up to 28 days. These doses were subsequently used in phase 2 and 3 clinical trials. Depending on the indication studied, two dosing regimens of vorapaxar, with and without a loading dose, have been evaluated. For NSTE ACS patients with planned PCI, as well as those with high-risk features, a 40-mg loading dose, followed by a 2.5-mg daily maintenance dose, has been shown to be safe and effective. In patients with established CAD, vorapaxar 2.5 mg daily without a loading dose has also been shown to be safe and effective for secondary prevention of ischemic events.

**Cost**

The estimated cost of vorapaxar is not yet available. It is probable, however, that the price will be additive to that of standard therapy (i.e., aspirin and clopidogrel) for the indications studied.

**Conclusion**

Vorapaxar is a competitive and selective inhibitor of PAR-1. It is metabolized by the CYP3A4 enzyme, and it interacts with both CYP3A4 inhibitors (e.g., ketoconazole) and CYP3A4 inducers (e.g., rifampin).

Based on the results of two phase 2 trials, it appears that vorapaxar is well tolerated when administered orally to patients undergoing non-urgent PCI, patients with NSTE ACS who are receiving standard-of-care antiplatelet therapy and are scheduled for PCI, and patients with a history of ischemic cerebral infarction who are receiving aspirin. Vorapaxar was not associated with an increased risk of bleeding when it was added to standard-of-care therapy. The efficacy and long-term safety of vorapaxar were the focus of two phase 3 studies (TRA 2P-TIMI 50 and TRA-CER). Based on recommendations from the studies’ respective DSMBs, TRA 2P-TIMI 50 was terminated early in 25% of the enrolled patients (those who experienced a stroke before or during the trial); TRA-CER was terminated in all patients. The results of the TRA 2P-TIMI 50 trial are highly anticipated, as therapy was continued in patients who experienced a spontaneous MI or PVD.

It is unclear whether these and future safety data will delay the FDA’s approval of vorapaxar, which is expected in 2012. Additional safety data may be necessary to ensure appropriate patient selection before vorapaxar receives final approval. The health care community eagerly awaits ongoing updates to the status of this promising, novel antiplatelet agent.

**References**


