Print ISSN 2319-2003 | Online ISSN 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

doi: 10.5455/2319-2003.ijbcp20150206

New Drug Update

Vorapaxar, a novel oral antiplatelet drug

Kranti Tekulapally*

Department of Pharmacology, Malla Reddy Medical College for Women, Hyderabad, India

Received: 21 November 2014
Accepted: 16 December 2014

***Correspondence to:**
Dr. Kranti Tekulapally,
Email: dr_t_kranti @ yahoo.com

ABSTRACT

Vorapaxor is first in the class of protease activated receptor 1 (PAR 1) antagonists. It acts by inhibiting the binding of thrombin to PAR 1 and thereby prevents platelet aggregation. USFDA approved it in May 2014 as the results of clinical trials showed that the benefit: risk ratio was high. It is to be used in a dose of 2.5 mg once daily as triple antiplatelet therapy with aspirin and clopidogrel for reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction or peripheral arterial disease. Increase in the incidence of intracranial hemorrhage is the major side-effect seen.

Keywords: Vorapaxar, Protease activated receptor 1 antagonsit, Thrombin receptor antagonist

INTRODUCTION

Acute coronary syndrome (ACS) comprises the spectrum of cardiac ischemic diseases from unstable angina to acute myocardial infarction. The key pathogenetic feature in ACS is formation of platelet rich atherosclerotic thrombi. Antiplatelet drugs are thus the major group of anti-thrombic drugs used in the management of ACS. The clinically important antiplatelet drugs available are aspirin, thienopyridines such as ticlopidine, clopidogrel, and prasugrel. Current American College of Cardiology/ American Heart Association guidelines recommend dual antiplatelet therapy with aspirin and clopidogrel for a minimum of 12 months in all ACS patients.[1] Despite regular treatment, the risk of ischemic recurrences remains high. Therefore, there is a need for improved therapeutic approaches for secondary prevention in ACS.

Thrombin is a potent platelet activator that acts through proteolytic cleavage of cell surface protease activated receptors (PARs). Four PARs were identified (PAR 1-4) of which PAR 1, PAR 3 and PAR 4 are activated by thrombin while PAR 2 is activated by trypsin.[2] PAR 1 is widely expressed on platelets and is activated at low thrombin concentrations. PAR 1 blockade may produce potent antiplatelet effects without affecting the ability of thrombin to generate fibrin and without inhibiting platelet activation by collagen.[3] It is also found that PAR 1 gene expression is upregulated at sites of vascular injury and in human atherosclerotic tissues, and it plays a significant role in vascular repair process.[4]

PAR 1 antagonists have a potential role in the prevention of atherosclerotic coronary artery disease. Vorapaxar is first in the class of PAR 1 antagonists.

MECHANISM OF ACTION

Vorapaxar is a synthetic tricyclic 3 phenylpyridine analog of natural product, himbacine. Himbacine is a complex piperidine alkaloid obtained from the bark of Australian magnolias.[5]

Vorapaxar is a slow, selective and reversible inhibitor of PAR 1. It prevents binding of thrombin to PAR 1 and

subsequently the downstream signaling pathway leading to platelet activation is prevented. It produces dose dependent platelet inhibition without affecting bleeding times and clotting times.[4]

PHARMACOKINETICS AND DOSAGE

Vorapaxar is absorbed rapidly and completely from the gut, its oral bioavailability is thus 100%. The peak plasma levels are reached in 1-2 hrs. Its half-life is 159-311 hrs.[4] It is extensively bound to serum albumin (~99.8%) and does not preferentially distribute into red blood cells. Vorapaxar is predominantly metabolized by CYP3A4 and to some extent by CYP2J2 to form two metabolites, M20 that is active circulatory metabolite and M19 that is predominant in excreta. Elimination is mainly through feces with minor renal excretion (<5% of the dose). No dose adjustment is required for age, gender, renal function[6] and mild to moderate hepatic impairment.[7] Ethnic differences in pharmacokinetics and pharmacodynamics were not observed in healthy Japanese and Caucasian subjects.[8] There is no known antidote for vorapaxar overdose.[9]

The recommended oral dose of vorapaxar is 2.5 mg once daily with or without food.

CLINICAL TRIALS

Two phase III trails were conducted to evaluate if addition of vorapaxar to the standard care alters the incidence of atherosclerotic population.

Thrombin receptor antagonist (TRA) vorapaxar in ACS trial

In this multinational, double blind trial, 12,944 patients with ACS without ST segment elevation were randomized to receive vorapaxar 40 mg loading dose, followed by 2.5 mg/day or placebo. The primary end point was a composite of death from cardiovascular causes, myocardial infarction, stroke and recurrent ischemia with rehospitalization. The trial was terminated early after a safety review. The results showed that the addition of vorapaxar to standard therapy did not significantly reduce the primary end points, but significantly increased the risk of major bleeding, including intracranial hemorrhage.[10]

TRA in the secondary prevention of atherosclerotic ischemic events (TRA-2P-TIMI 50 trial)

In this trial 26,449 patients who had a history of myocardial infarction, ischemic stroke or peripheral arterial disease were randomized to receive either vorapaxar 2.5 mg daily or a placebo and were followed for a median of 30 months. The primary efficacy end point was the composite of death from cardiovascular causes, myocardial infarction or stroke. Due to increased risk of intracranial hemorrhage, the data and safety monitoring board recommended discontinuation of the study treatment in patients with a history of stroke. The results of this TRA-2P-TIMI 50 trial showed that vorapaxar reduced the risk of cardiovascular death or ischemic events in patients with stable atherosclerosis who were receiving standard therapy but at the expense of increasing the risk of severe bleeding including intracranial hemorrhage.[11]

Current status

USFDA approved vorapaxar in May 2014 for reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction or peripheral arterial disease in a dose of 2.5 mg once daily as triple antiplatelet therapy with aspirin and clopidogrel. It is not yet available in India.

Adverse effects

Vorapaxar is generally well-tolerated. Bleeding is the most common adverse effect reported in the form of epistaxis and intracranial hemorrhage. Non bleeding side-effects are infrequent.[10,11]

Contraindications

- History of stroke or transient ischemic attack
- Patients who are on CYP3A4 inducers or inhibitors
- Patients with acute pathological bleeding like intracranial hemorrhage
- Severe hepatic impairment.

Drug interactions

Concurrent administration of CYP3A4 inhibitors like ketoconazole increase the plasma concentration of vorapaxar while CYP3A4 inducers like rifampicin decrease it. Ketoconazole increased area under curve and Cmax of vorapaxar by two-fold while rifampicin decreases it by 50%.[12]

No clinically significant reactions were found when warfarin was coadministered.[13]

SUMMARY

Vorapaxar is a novel antiplatelet agent which acts by inhibiting thrombin receptor, PAR 1. Since the clinical trials proved that its benefits were more than risks, USFDA approved it in May 2014. It is to be used in a dose of 2.5 mg daily along with other antiplatelet agents. It significantly reduces the risk of thrombotic cardiovascular events in all patients with a history of myocardial infarction or peripheral arterial disease but at the expense of increasing the risk of severe bleeding including intracranial hemorrhage.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Christopher P, Braunwald E. Unstable angina and non ST segment elevation myocardial infarction. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 18th Edition. New York: McGraw Hill; 2012: 2015-21.
2. Olivier D, Carlos U, Martin S, Nigel W. Proteinase-activated receptors: novel mechanisms of signaling by serine proteases. Am J Physiol. 1998;274(6):1429-52.
3. TRA*CER Executive and Steering Committees. The Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRA*CER) trial: study design and rationale. Am Heart J. 2009;158(3):327-34.e4.
4. Kosoglou T, Reyderman L, Tiessen RG, van Vliet AA, Fales RR, Keller R, et al. Pharmacodynamics and pharmacokinetics of the novel PAR-1 antagonist vorapaxar (formerly SCH 530348) in healthy subjects. Eur J Clin Pharmacol. 2012;68(3):249-58.
5. Chackalamannil S, Davies RJ, Wang Y, Asberom T, Doller D, Wong J, et al. Total Synthesis of (+)-Himbacine and (+)-Himbeline. J Org Chem. 1999;64(6):1932-940.
6. Kosoglou T, Kraft WK, Kumar B, Statkevich P, Xuan F, Ma L, et al. Pharmacokinetics and pharmacodynamics of the novel PAR-1 antagonist vorapaxar in patients with end-stage renal disease. Eur J Clin Pharmacol. 2012;68(7):1049-56.
7. Statkevich P, Kosoglou T, Preston RA, Kumar B, Xuan F, Trusley C, et al. Pharmacokinetics of the novel PAR-1 antagonist vorapaxar in patients with hepatic impairment. Eur J Clin Pharmacol. 2012;68(11):1501-8.
8. Kosoglou T, Reyderman L, Kasserra C, Jennings LK, Young S, Xuan F, et al. No differences in the pharmacodynamics and pharmacokinetics of the thrombin receptor antagonist vorapaxar between healthy Japanese and Caucasian subjects. Eur J Clin Pharmacol. 2012;68(3):291-300.
9. Macaulay TE, Allen C, Ziada KM. Thrombin receptor antagonism -the potential of antiplatelet medication SCH 530348. Expert Opin Pharmacother. 2010;11(6):1015-22.
10. Tricoci P, Huang Z, Held C, Moliterno DJ, Armstrong PW, Van de Werf F, et al. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. N Engl J Med. 2012;366(1):20-33.
11. Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. N Engl J Med. 2012;366(15):1404-13.
12. Kosoglou T, Statkevich P, Kumar B, Xuan F, Schiller JE, Johnson-Levonas AO, et al. The effect of multiple doses of ketoconazole or rifampin on the single- and multiple-dose pharmacokinetics of vorapaxar. J Clin Pharmacol. 2013;53(5):540-9.
13. Kosoglou T, Zhu Y, Xuan F, Black L, Johnson-Levonas AO, Martinho M, et al. Vorapaxar, an oral PAR-1 receptor antagonist, does not affect the pharmacokinetics and pharmacodynamics of warfarin. Eur J Clin Pharmacol. 2012;68(11):1509-16.

doi: 10.5455/2319-2003.ijbcp20150206
Cite this article as: Tekulapally K. Vorapaxar, a novel oral antiplatelet drug. Int J Basic Clin Pharmacol 2015;4:188-90.