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Vorapaxar: A New Antiplatelet Therapy

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Abstract

Antiplatelet therapy plays an integral role in the treatment of ischemic heart disease, the leading cause of death in most Western Countries. Previously, the classes of antiplatelet drugs that proved effective included aspirin, thienopyridines (e.g.ticlopidine, clopidogrel, prasugrel), a non-thienopyridine (ticagrelor), and glycoprotein (GP) IIb/IIIa receptor antagonists (e.g. abciximab, eptifibatide, tirofiban). Administration of antiplatelet therapy typically included dosages of acetylsalicylic acid alongside either a thienopyridine or non-thienopyridine ADP receptor inhibitor. Particular combinations within this dual antiplatelet therapy were contingent on specific needs and occurrences of patients. Inherent limitations of these antiplatelet drugs, however, lead inevitably to the development of new agents that not only conquer said limitations but also possess new, more efficient mechanistic modes of action. Vorapaxar functions as a thrombin receptor antagonist, working against the protease activated receptor PAR-1 to inhibit platelet aggregation without affecting hemostasis.

Keywords: Antiplatelet therapy; Vorapaxar; PAR-1

Antiplatelet therapy plays an integral role in the treatment of ischemic heart disease, the leading cause of death in most Western Countries. Previously, the classes of antiplatelet drugs that proved effective included aspirin, thienopyridines (e.g. ticlopidine, clopidogrel, prasugrel), [1] a non-thienopyridine (ticagrelor), [2] and glycoprotein (GP) IIb/IIIa receptor antagonists (e.g. abciximab, eptifibatide, tirofiban). Administration of antiplatelet therapy typically included dosages of acetylsalicylic acid alongside either a thienopyridine or non-thienopyridine ADP receptor inhibitor [3]. Particular combinations within this dual antiplatelet therapy were contingent on specific needs and occurrences of patients [4]. Inherent limitations of these antiplatelet drugs, however, lead inevitably to the development of new agents that not only conquer said limitations but also possess new, more efficient mechanistic modes of action. Vorapaxar functions as a thrombin receptor antagonist, working against the protease-activated receptor PAR-1 to inhibit platelet aggregation without affecting hemostasis.

The inhibition of platelet receptors has proven strategic in the suppression of platelet aggregation. Past antagonists inhibited multiple receptors including ADP receptors, thromboxane receptors, and the glycoprotein (GP) IIb/IIIa receptor directly responsible for platelet aggregation. Ticagrelor, the non-thienopyridine, was, until recently, hailed as the most potent platelet inhibitor. Ticagrelor binds reversibly to the ADP receptor, P_2Y_{12}, and does not require metabolic activation. Despite overcoming most of the limitations of its predecessors, questions about the efficacy of Ticagrelor remained unanswered [5]. Further developments in antiplatelet therapy followed.

The most crucial platelet receptors are the protease-activated receptors (i.e. PAR-1, PAR-4). Protease-activated receptors, alone, are capable of initiating platelet aggregation. Furthermore, these receptors account for the majority of thrombin-induced signaling [6]. Thrombin is the most potent, naturally produced platelet agonist; its role in the pathophysiology of thrombosis is unparalleled. Consequently, its antagonism provides a potential mechanism that routs all others.

Vorapaxar, a non-protein structure, is an oral agent that operates with a high selectivity toward PAR-1 inhibition. PAR-1, also known as thrombin receptor, is the prototypical protease-activated receptor and is widely distributed in human platelets, endothelial cells, and smooth muscle cells [7]. It belongs to the family of seven transmembrane G-protein coupled receptors. Thrombin activation of PAR-1 incorporates a unique mechanism. It binds to PAR-1 through its exo-anion binding site and causes the cleavage of the extracellular domain at Arginine 41-Serine 42. This cleavage, naturally, reveals a new N-terminus that serves as a tethered ligand. This ligand S42FLLRN (serine-phenylalanine-leucine-leucine-arginine-asparagine) binds intramolecularly, producing a cytoplasmic signaling cascade. Vorapaxar acts to inhibit this action with proven efficacy. Furthermore, vorapaxar is not a pro-drug, it does not require enzymatic activation, and has an efficient half-life of 159-311 hours. These added characteristics, along with its rapid onset of action (within 1-2 hours), further separate vorapaxar from previous anti-platelet drugs [8].

Vorapaxar's inhibition of PAR-1 has shown tremendous promise in the suppression of platelet aggregation and concomitant prevention of myocardial infarction and stroke. Developed by Merck & CO, it received its FDA approval in the U.S. on May 5, 2014. The results of the phase II and phase III trials were as follows: Vorapaxar (Zontivity) has optimal effectiveness when administered to stable atherosclerotic patients with histories of peripheral arterial disease and myocardial infarction. Additionally, patients who had previously taken thienopyridines had a higher risk of bleeding than those who began a thienopyridine at randomization. Lastly, patient selection is critical as findings also included increased bleeding for patients of advanced age and/or low body weight. Risks include moderate to severe bleeding and stroke.

When dual antiplatelet therapy is indicated, vorapaxar has proven to contribute advantageously to the reduction of thrombotic cardiovascular events. It has not yet been tested as an effective

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antiplatelet monotherapy, but should be used in association with aspirin or in addition to a dual therapy. It would be interesting to perform studies juxtaposing the individual efficacy of vorapaxar with that of aspirin and/or clopidogrel. Today, however, in the prevention and regulation of ischemic heart disease, vorapaxar should be considered an indispensable addition to antiplatelet therapy.

References

1. Hashemzadeh M, Goldsberry S, Furukawa M, et al. (2009) ADP receptor-blocker Thienopyridines: Chemical structures,Mode of action and Clinical Use. A review. J Invasive Cardiol 21: 406-412.
2. Ramraj R, Movahed MD, Hashemzadeh M (2011) Novel Antiplatelet Agent Ticagrelor in the Management of Acute Coronary Syndrome.J Interv Cardiol 24: 199-207.
3. Goto S, Tomita A (2014) New antithrombotics for secondary prevention of acute coronary Syndrome. Clin Cardiol 37: 178-187.
4. Cairns JA, McMurtry MS (2013) Oral antithrombotic therapy in atrial fibrillation associated with acute or chronic coronary artery disease. Can J Cardiol 29: S60-S70.
5. Dobesh PP, Oestreich JH (2014) Ticagrelor: Pharmacokinetics, Pharmacodynamics, Clinical Efficacy and Safety. Pharmacotherapy 34: 1077-1090.
6. Rivera J, Lozano M, Navarro-Nuñez L, Vicente V, et al (2009) Platelet receptors and signaling in the dynamics of thrombus formation. Haematologica 94: 700-711.
7. Lee H, Hamilton JR (2012) Physiology, pharmacology, and therapeutic potential of proteaseactivated receptors in vascular disease. Pharmacol Ther 134: 246-259.
8. Abdulsattar Y, Ternas T, Garcia D. (2011) Vorapaxar: Targeting a Novel Antiplatelet Pathway. P&T 36: 564-568.

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