The Novel Protease-Activated Receptor 1 Antagonist Vorapaxar as a Treatment for Thrombosis in Afibrinogenemia

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Afibrinogenemia is a rare disorder characterized by the absence of detectable fibrinogen due to genetic mutations.1 The common presentation is spontaneous or unusual bleeding with minor trauma. But the recent case report and review by Santoro et al highlights that many patients present with thrombosis with or without bleeding, representing challenging clinical situations.2 Here, we add insight into management of these patients with a case of a patient with afibrinogenemia who developed recurrent arterial stenosis refractory to dual antiplatelet therapy and fibrinogen replacement treated with the novel protease-activated receptor 1 (PAR-1) antagonist vorapaxar.

Fibrinogen is a glycoprotein that is produced in the liver and stored in platelet α granules after uptake from plasma.1 Fibrinogen functions in fibrin clot formation, thrombin regulation, platelet aggregation, and fibrinolysis. Afibrinogenemia is an autosomal recessive disorder associated with a quantitative deficiency of fibrinogen and a prevalence of 1 in 1,000,000.3 The clinical manifestations of afibrinogenemia include umbilical cord hemorrhage and bleeding in the gastrointestinal (GI) tract, genitourinary tract, mucosa, skin, and the central nervous system.4 Approximately 30% of patients with afibrinogenemia may also have thrombotic complications due to the antithrombin function of fibrinogen. Rarely patients may have both bleeding and thrombotic complications related to the disease.5,6 Treatment for hemorrhage includes antifibrinolytics and/or fibrinogen replacement therapy with fresh frozen plasma, cryoprecipitate, and plasma-derived fibrinogen concentrate.7 In the setting of a thrombotic phenotype, there is no clear consensus, but treatment with low molecular weight heparin, antplatelet agents, vasodilators, lepirudin, and direct thrombin inhibitors with fibrinogen replacement therapy has been used.8 We present a case of a patient with bleeding and thrombotic complications associated with congenital afibrinogenemia treated with the novel PAR-1 antagonist vorapaxar (Zontiv-


Publisher

Thieme Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.

Multiple agents inhibit platelet activation but only vorapaxar inhibits protease-activated receptor 1 (PAR-1). Platelet activation pathways and drug molecular targets. Thrombin binds to PAR-1, which leads to shape change, phospholipase C (PLC) activation, thromboxane A2 (TxA2) generation, and activation of the glycoprotein (GP) IIb/IIIa receptor, resulting in sustained platelet aggregation. Cyclooxygenase 1 (COX-1) catalyzes the production of TxA2, a potent platelet aggregator, generated by platelets activated by thrombin and other agonists. Adenosine 5′-diphosphate (ADP) binds to its 7-transmembrane domain receptors, P2Y1 and P2Y12, to activate platelets. P2Y1 is coupled to Gaq and G12. Gaq is linked to a signaling pathway involving PLC activation, resulting in a rise in the intracellular calcium concentration ([Ca^2+]i) and protein kinase C (PKC) activation, leading to GP IIb/IIIa activation and transient platelet aggregation. G12 mediates platelet shape change. P2Y12 is linked to Gai-coupled signaling cascades associated with adenyl cyclase (AC) downregulation and decreased cyclic-3′,5′-monophosphate (cAMP) production, which mediates GP IIb/IIIa receptor activation, leading to sustained platelet aggregation. (Reproduced with permission of Di Minno MND, Guida A, Camera M, Colli S, Di Minno G, Tremoli E. Overcoming limitations of current antiplatelet drugs: a concerted effort for more profitable strategies of intervention. Ann Med 2011;43(7):531–544, under open access license https://creativecommons.org/licenses/by/2.0/legalcode with no alterations.)

Vorapaxar is a competitive and selective antagonist of PAR-1 thrombin receptor on platelets. In a randomized, double-blind, placebo-controlled trial (TRA2°P-TIMI 50) of vorapaxar, patients with a history of myocardial infarction, ischemic stroke, or peripheral arterial disease (PAD) were randomized to vorapaxar or placebo. Vorapaxar reduces acute limb ischemia in patients with symptomatic PAD. Our patient was started on vorapaxar as an antiplatelet therapy for increased thrombin activity, which was thought to be causing thrombosis and stenosis. If the development of thrombosis in patients with congenital afibrinogenemia is secondary to excess thrombin, then blockade of PAR-1 with this new antiplatelet agent would be a rational therapy. As there is an increased risk of bleeding with the antiplatelet agents, fibrinogen replacement would need to be determined on a case-by-case basis. While vorapaxar activity on platelet aggregation has been evaluated, the effect on endothelial cells and smooth muscle cells has not been studied and is an area for further research.

In conclusion, vorapaxar targets the thrombin pathway and is a reasonable treatment option for refractory thrombosis in patients with afibrinogenemia. Further research will need to focus on management strategies of these complex patients.
Conflict of Interest
The authors have no conflict of interest to disclose.

References
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Fig. 3  Bilateral intra-abdominal stent stenosis (White arrows).