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, antiplatelet 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-
clopidogrel and aspirin. Clopidogrel was discontinued and she was started on vorapaxar 2.08 mg PO QD, and the same dose of aspirin was continued. Surveillance angiogram 6 and 12 months after starting vorapaxar revealed patent infrarenal stents bilaterally and improved multifocal plaques in the left and right common iliac arteries. The plan was to discontinue vorapaxar after 12 months of therapy, but given patient’s response and tolerability to the therapy, it has been continued to date.

Treatment recommendation per the 2016 Delphi consensus in patients with bleeding phenotype of a fibrinogenemia is to start secondary prophylaxis after first life-threatening bleeding episode. Fibrinogen replacement therapy is a risk factor for thromboembolism, although the exact incidence of events associated with the treatment is unknown. In patients with thrombosis, fibrinogen replacement therapy should be administered concurrently with low molecular weight heparin. For patients on antiplatelet therapy, fibrinogen replacement should be considered based on the risk of bleeding. Our patient had a history of Gi bleeding and therefore she was continued on replacement therapy for the duration of antiplatelet therapy. The proposed mechanism for the development of thrombosis in patients with congenital a fibrinogenemia is lack of antithrombin I activity of fibrin. Normally, this activity of fibrin includes sequestering free thrombin, which downregulates thrombin activity and decreasing subsequent platelet activation. But in patients with a fibrinogenemia, free thrombin is not sequestered, and increasing levels of free thrombin lead to platelet activation through the PAR-1 and a prothrombotic state. In addition, increasing thrombin promotes proliferation of vascular smooth muscle cells, which may have contributed to stenosis in this patient. PAR-1 is found on the surface of platelets and vascular endothelium. Thrombin levels were not measured in this patient, but her episodes of limb pain improved with fibrinogen replacement therapy, which highlights the possibility of elevated thrombin activity as the cause and reduction of its activity when fibrinogen was replaced.

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 a fibrinogenemia 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 a fibrinogenemia. Further research will need to focus on management strategies of these complex patients.
Fig. 3  Bilateral intra-abdominal stent stenosis (White arrows).

Conflict of Interest
The authors have no conflict of interest to disclose.

References
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