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Literature Seminar

When: February 4, 2021
Time: 2:30 PM
Location: Microsoft TEAMS

Novel strategies for treatment of hemophilia A and B

Abstract

Hemophilia is one of the most common types of bleeding disorders and is categorized into types A and B. [1] Hemophilia A (HemA) is caused by deficiency or absence of the clotting factor, FVIII, whereas Hemophilia B (HemB) is associated with FIX.[2] To date, the most widely used and preferred prophylactic treatment for Hemophilia is replacement factor (rFVIII or rFIX), but the downside of this drug approach is its short half-life which then requires twice or thrice intravenous administrations per week. In this seminar, three novel treatments will be introduced: (1) an improved replacement FVIII, (2) an inhibitor of the anticoagulation pathway, and (3) FXIII cotreatment. The first treatment is BIVV001, a new bioengineered replacement factor for HemA that exhibits twice the half-life of standard rFVIII. The primary reason for the short half-life of endogenous and recombinant FVIII is its dependency on its own chaperone, the von Willebrand factor (VWF) which forms a complex with FVIII upon circulation in plasma.[3] BIVV001 is independent of VWF, attached with biodegradable XTEN polypeptides, and fused with dimeric Fc domains which all contributed to extended half-life.[4] The second treatment which applies both to HemA and HemB targets the anticoagulation pathway by inhibiting Activated Protein C (APC) with double lysine variants of the inhibitors PCI and α_1-Antitrypsin. With APC inhibited, thrombin generation levels increase eventually leading to higher levels of FVIII or FIX.[5]. The third treatment aims to strengthen the clot formation through cotreatment of FXIII with the hemostatic agent FVIII. This cotreatment generated an increase not only in fibrin γ-γ formation, α_2-antiplasmin crosslinks, but also on the fibrin α chain crosslinks making the hard clot more stable and resistant from proteolysis.[6] In summary, these novel treatments target different pathways in the blood coagulation cascade by increasing the half-life of coagulation FVIII in the Tenase complex using BIVV001, employing APC inhibitors to prolong the Prothrombinase complex, and/or cotreatment with FXIII to improve crosslinks in clot formation.

References:

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3. Peters, R. *et* al. *Blood*. 2020, *135*(17), 1484–1496.
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5. Polderdjik, S., Adams, T., Ivanciu, L., Camire, R., Trevor, B., Huntington, J. et al, *Blood*. 2019, *129*(1), 105-113.
6. Beckman J., Holle L., Wolberg, A. *J Thromb Haemost.* 2018, *16*(1), 131–41.