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Aptamers Targeting Von Willebrand Factor: What and Why?

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Aptamers are increasingly being investigated as therapeutic drugs in cancer, infectious diseases, and cardiovascular disease.[1] Aptamers are small single stranded DNA or RNA molecules that bind to a specific target. As such, they reflect the working mechanism of an antibody. The difference between them is that aptamers are composed of nucleic acids (oligonucleotides) and antibodies of amino acids (proteins). Aptamers are more stable than antibodies, have longer shelf lives, are more specific with higher affinity, have an animal free production line, and are easier to produce.[2]

Recently, aptamers have been investigated in the field of thrombosis and hemostasis, especially for interference with the function of von Willebrand factor (VWF) (Figure 1). Several aptamers have been designed to recognize and bind the A1 domain of VWF, leading to interference with the interaction of the platelet GPIB/IX/V receptor. This platelet-VWF interaction is crucial for normal hemostasis. Pathological increased binding can lead to certain hematological disorders such as thrombotic thrombocytopenic purpura (TTP) or type 2B von Willebrand disease (VWD). In these circumstances, designated aptamers might have the potential to restore normal hemostasis. On the other hand, downregulating normal platelet–VWF interaction might be of importance for cardiovascular disease in protection of atherothrombosis. Last, recent developments in designing aptamers with longer half-lives appeared to have a striking effect on the half-life of VWF itself.

APTAMERS IN TTP

The hallmark of TTP is the presence of ultra large VWF multimers leading to spontaneous binding of platelets through interaction with the platelet GPIB/IX/V receptor with the A1 domain of VWF. ARC1779 is an aptamer that recognizes this A1 domain of VWF and therefore interferes with platelet binding. It has been suggested to be a promising novel therapeutic for the treatment of TTP more than 10 years ago.[4] A clinical trial confirmed that suppression of VWF activity correlated with plasma concentrations of ARC1779 and recovered with tapering and discontinuing the ARC1779 infusion.[5] However, this trial was prematurely stopped due to sponsor-related financial issues. ARC15105 was the successor to the short-acting ARC1779 and was shown to inhibit VWF activity >90% in blood samples taken 300 hours after a single intravenous or subcutaneous dose in monkeys.[6] No further clinical trials development have been seen since. TAGX-0004 is a more recent aptamer targeting the same A1 domain. In vitro, TAGX-0004 showed stronger inhibition than ARC1779 and had comparable inhibitory effects to caplacizumab.[7] Although caplacizumab is currently being used in first line therapy of TTP, TAGX-0004 has the potential to be developed further and be a competitor in this field although a clinical trial program is not yet established.

APTAMERS IN VON WILLEBRAND DISEASE

ARC1779 was investigated in type 2B VWD, a bleeding disorder with pathological A1 domain-platelet interaction, in 2010.[8] ARC1779 prevented desmopressin-induced thrombocytopenia in these patients. In addition, ARC1779 substantially enhanced the desmopressin-induced maximal increase in VWF parameters and improved multimer patterns.

BT200 is another A1-domain binding RNA aptamer and an optimized derivative of ARC1779. It effectively inhibited VWF activity in the blood of stroke patients, in a target concentration-dependent manner.[9] BT200 is a pegylated form of its predecessor and its activity can be rapidly reversed by the complementary aptamer BT101.[10] Recently, BT200 (now called rondoraptivon pegol) was given to patients with type 2B VWD.[11] It rapidly corrected thrombocytopenia, the

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HemaSphere (2023) 7:2(e830). http://dx.doi.org/10.1097/HS9.0000000000000830.

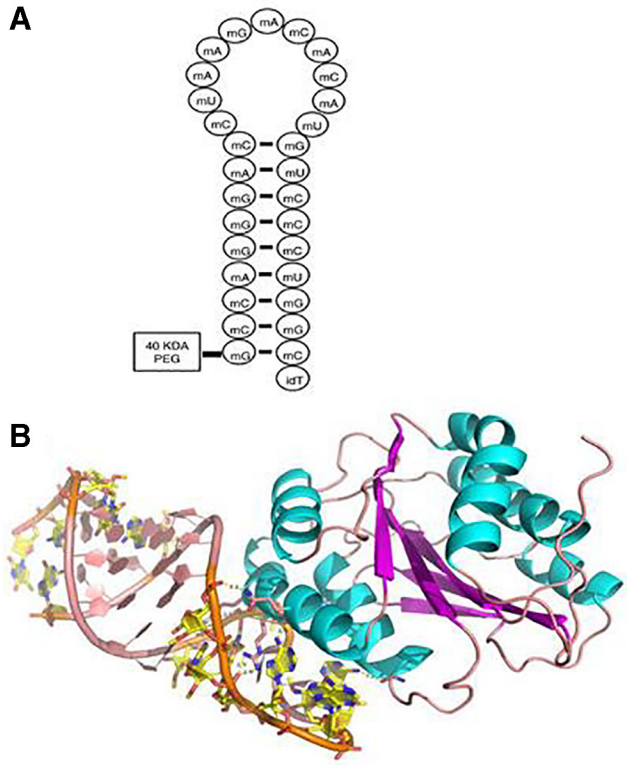

Figure 1. The aptamer BT200 in relation to von Willebrand factor. (A) Secondary structure of BT200. (B) Cocrystal structure of the unpegylated aptamer BT100 with the von Willebrand factor A1 domain (from Zhu et al[3]).

VWF antigen increased from 64% to 143%, FVIII increased from 67% to 134%, and VWF activity (ristocetin) increased from 17% to 48%. Intermediate and high molecular weight VWF multimers were restored.

APTAMERS IN HEMOPHILIA

Interestingly, although originally designed to inhibit platelet adhesion to VWF, BT200 increased VWF antigen levels and FVIII activity up to 4-fold above baseline in healthy volunteers, which is explained by decreased clearance of VWF.[12] Apparently, pegylation of VWF A1 domains decreases their clearance by the macrophage LRP1. As the half-life of factor VIII (FVIII) is strongly dependent on that from VWF, rondoraptivon pegol could have a major impact in patients with hemophilia A as well. This was recently tested in 19 hemophilia patients.[13] With weekly subcutaneous injections, median factor VIII (FVIII) increased from 22% to 48% in patients with mild hemophilia and from 3% to 7.5% in moderate hemophilia. In patients with severe hemophilia, the half-life of infused FVIII increased from 10.4 to 31.1 hours. One week after the last subcutaneous injection of rondoraptivon pegol, plasma levels of VWF antigen increased from a median of 97% at baseline to 323% on day 35 and returned to normal on day 56. In contrast, the VWF activity was only mildly affected, which reflects the double edged sword of increasing antigen levels and inhibiting functional properties at the same time.

STROKE

VWF plays a crucial role in the initial steps of platelet plug formation on the vessel wall. Therefore, targeting VWF is focus of interest in atherothrombotic cardiovascular disease. The DTRI-031 aptamer (also preventing platelet binding to VWF) has been shown to be a potent antithrombotic agent in a murine carotid artery injury thrombosis model.[14] In a canine stroke model using large vessel occlusion (LVO), DTRI-031 effectively recanalized LVO after 6 hours of stroke onset with reduced infarct volume and no incidence of hemorrhage.[15] Moreover, this aptamer was designed so that its activity can be reversed by an antidote oligonucleotide. Indeed, platelet function and hemostasis were restored in less than 5 minutes, which represents a major safety advance for an antiplatelet agent. A phase 1 trial in healthy volunteers has recently been completed, a phase 2 program is planned to be initiated soon with BB-031 as the new name.

In conclusion, aptamers targeting the A1 domain of VWF are a new class of drugs that have the potential to have a major impact on the treatment of several VWF-related coagulation disorders.

DISCLOSURES

REGS has received research funding from Bayer, CSL Behring, NovoNordisk. OctaPharma, Sanofi and Sobi (all to institution).

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