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MEETING ABSTRACT Open Access

Inhibition of tissue factor pathway inhibitor (TFPI) by ARC19499 improves clotting of hemophiliac blood

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Background

Hemophilia A and B are disorders resulting from a deficiency in factor VIII (FVIII), and factor IX (FIX), respectively. Tissue Factor (TF) is a key component of the extrinsic pathway and plays a role in the coagulation defect of hemophilic blood. Neutralizing the activity of TFPI represents a promising treatment concept in patients with hereditary or acquired hemophilia. ARC19499 is a polyethylene glycol (PEG)-conjugated aptamer that binds to TFPI and inhibits its function as a negative regulator of coagulation.

Methods

We evaluated the effect of the anti-TFPI aptamer ARC19499 on thrombin generation and clot formation in 40 hemophilia patients (congenital hemophilia: 29 adults, 10 children, one acquired hemophilia patient) and 27 healthy male controls. Concentration-effect curves of ARC19499 were assessed by the calibrated automated thrombogram (CAT) and rotational thrombelastometry (ROTEM) with and without corn trypsin inhibitor (CTI) in whole blood and platelet-poor plasma.

Results

Clotting patterns were significantly compromised in patients vs. controls. Measured FVIII:C levels in hemophiliacs correlated with parameters of the CAT assay (except lag time) and also with the clotting time assessed by ROTEM. ARC19499 had a concentration-dependent pro-hemostatic effect in CAT and ROTEM. ROTEM results with and without CTI were consistent. ARC19499 normalized ROTEM clotting parameters and rendered CAT patterns of hemophilia patients practically indistinguishable from those of controls. In patients, ARC19499 normalized the endogenous thrombin potential, time-to-peak and the start tail, and increased peak thrombin more than 2-fold. ARC19499 raised peak thrombin in patients with FVIII:C under 1% to levels within the range of healthy controls and higher than baseline in patients with FVIII:C above 5%. Effective concentrations of ARC19499 started at 2 nM. In an acquired hemophilia patient ARC19499 worked synergistically with activated prothrombin-complex concentrate/factor VIII inhibitor bypass activity (FEIBA) pre-treatment. Similarly, in blood spiked with a FVIII antibody, simulating a state of acquired hemophilia, ARC19499 restored normal coagulation.

Conclusions

The anti-TFPI aptamer ARC19499 effectively enhanced coagulation in blood of patients with congenital or acquired hemophilia and therefore deserves further evaluation in clinical trials.

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