Session: Novel hemophilia treatments, pre-clinical

OC 21.3 - The in vitro and in vivo hemostatic efficacies of a novel FVIIIa-mimetic bispecific antibody, SS315, for the treatment of Hemophilia A.

Sunday, June 23, 2024 15:15 – 15:30 ICT Room: Ballroom B1

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Background: Hemophilia A (HA) is a genetic disorder characterized by factor VIII (FVIII) deficiency. A non-factor therapeutic, FVIIIa-mimetic bispecific antibody (BsAb) Emicizumab, was marketed worldwide including China for the treatment of HA. However, due to cost, it is not available for the majority Chinese patients. We have developed a novel symmetric FVIIIa-mimetic BsAb, SS315, by targeting FX with its upper Fab arms and FIXa with its down-side scFv arms, respectively (Fig. 1A,B), enhancing the catalyzing efficiency of FIXa and being functional at low concentration ranges, which could address a significant unmet clinic need for the HA patients in the developing countries.

Aims: To demonstrate the hemostatic potency of SS315 in vitro and in vivo.

Methods: The affinity was identified by bio-layer interferometry. The coagulation potency was measured by FXIa-activated thrombin generation assay. The hemorrhage-preventing capacity was examined by tail vein transection test in the FIX- and FX-humanized HA mice model. The hemostasis capacity was confirmed in FVIII-neutralizing antibody-induced acquired HA (AHA) Cynomolgus monkeys.

Results: The affinities of SS315 to hFIXa and hFX were < 1 nM. SS315 exhibited dose advantage over Emicizumab in hemostatic potency at low concentrations. Multiple intravenous doses of SS315 (0.25 - 8 mg/kg) effectively prevented bleeding in HA mice (Fig. 1C). Low doses of SS315 (0.5 - 1.0 mg/kg) achieves similar hemostatic effect with 3.0 mg/kg Emicizumab, suggesting a superior potency of SS315 over Emicizumab in vivo. Moreover, it was confirmed that low doses of SS315 (0.5 and 2.0 mg/kg) shortened activated partial thromboplastin time and reduced blood losses and bleeding times, achieving comparable efficacy of 3.0 mg/kg Emicizumab in AHA monkeys (Fig. 2).

Conclusion(s): Combining in vitro and HA/AHA animal models, the present study supports that SS315 can mimic the activity of FVIIIa to control bleeding and has a better pharmacologic profile than Emicizumab.