Effect of Mim8 and Emicizumab on Factor VIII Recovery by a Novel, Bovine Chromogenic FVIII Assay

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Introduction

Emicizumab and Mim8 are humanized bispecific antibodies that mimic activated factor VIII (FVIII) by bridging factor IXa/X to activate FX. Chromogenic FVIII assays containing human factor IXa/X proteins or hybrid human-bovine proteins demonstrate sensitivity to the presence of these antibodies while the effect on bovine chromogenic assays is reduced.[1]

Our objective was to evaluate the effect of emicizumab and Mim8 on measurements of native and recombinant FVIII (rFVIII) activity in plasma samples using multiple chromogenic FVIII assays (human and bovine).

Methods

Doses of Mim8 (0 to 20 µg/mL) and emicizumab (0 to 150 µg/mL) were spiked into congenital severe hemophilia A pooled plasma (N=6) containing native or rFVIII (ADVATE®) at target 5, 20 and 100% FVIII activity levels.

Samples were measured using a human (BIOPHEN™ FVIII:C (Hyphen Biomed)) and two bovine assays (Coatest® SP4 FVIII (Chromogenix) and a novel bovine CRYO*check*™ Chromogenic Factor VIII (Precision BioLogic)) on an IL ACL TOP 550.

Where the linear regression slope was significant, the interferent dose that did not exceed the allowable difference (±30% for 5% FVIII samples or ±20% for ≥20% FVIII) at the 95% confidence interval was calculated as per CLSI EP07–Third Edition.

Results

Across all sample levels, Mim8 and emicizumab interference was observed using the human based assay (BIOPHEN FVIII:C), out-of-chart data not presented.

Both bovine chromogenic assays accurately measured native and rFVIII at ≥5% FVIII in the presence of emicizumab **(Figure 1)** or Mim8 **(Figure 2)**.

Emicizumab did not show interference up to 150 µg/mL with both bovine chromogenic assays in all tested FVIII samples. Also, no interference was observed up to 20 µg/mL Mim8 for the bovine assays at 20 and 100% FVIII levels **(Table 1)**.

At 5% FVIII, the maximum dose of Mim8 without interference, depending on the FVIII source, ranged from 9 to 12 µg/mL for either bovine assay.

Conclusions

The novel bovine formulation of CRYO*check* Chromogenic Factor VIII reduced Mim8 interference across all FVIII levels relative to previously published data using the hybrid assay version.[2]

No interference was observed at the expected therapeutic concentration of 5 µg/mL Mim8[3] or the therapeutic concentration of 50 µg/mL emicizumab.[4]

Bovine chromogenic Factor VIII assays enable accurate FVIII measurement in the presence of FVIIIa mimetic bispecific antibodies.

Figure 1

Fold difference in FVIII activity of plasma containing native FVIII or Advate at target 5, 20 and 100% FVIII activity levels spiked with emicizumab at 0 to 150 µg/mL.

Five replicates of each sample were measured at 0, 25, 50, 75, 100 and 150 µg/mL of emicizumab using Coatest SP4 FVIII and CRYO*check* Chromogenic Factor VIII (bovine). The fold difference in activity at each dose of emicizumab relative to the 0 concentration dose for each sample is shown. The maximum allowable difference (1.3 fold for 5% FVIII or 1.2 fold for ≥20% FVIII) is indicated by the dotted lines.

*The therapeutic plasma level of emicizumab is approximately 50 µg/mL.

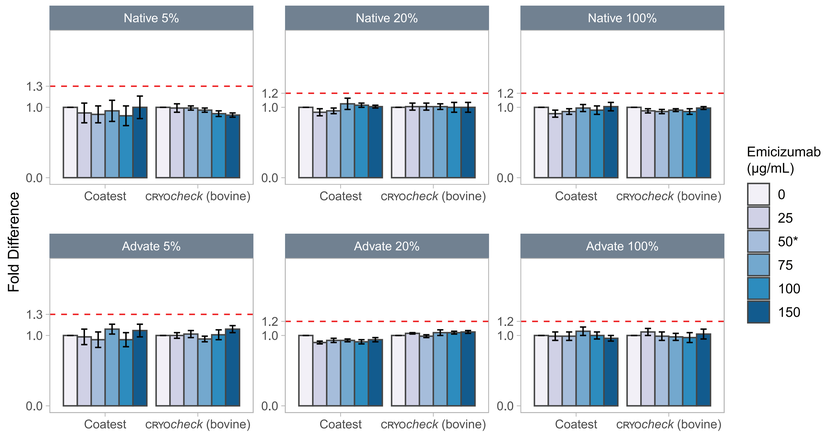

Figure 2

Fold difference in FVIII activity of plasma containing native FVIII or Advate at target 5, 20 and 100% FVIII activity levels spiked with Mim8 at 0 to 20 µg/mL.

Five replicates of each sample were measured at 0, 1, 2, 5, 8, 10, 15 and 20 µg/mL of Mim8 using Coatest SP4 FVIII and CRYO*check* Chromogenic Factor VIII (bovine). The fold difference in activity at each dose of Mim8 relative to the 0 concentration dose for each sample is shown. The maximum allowable difference (1.3 fold for 5% FVIII or 1.2 fold for ≥20% FVIII) is indicated by the dotted lines.

*The expected therapeutic plasma level of Mim8 is 5 µg/mL.

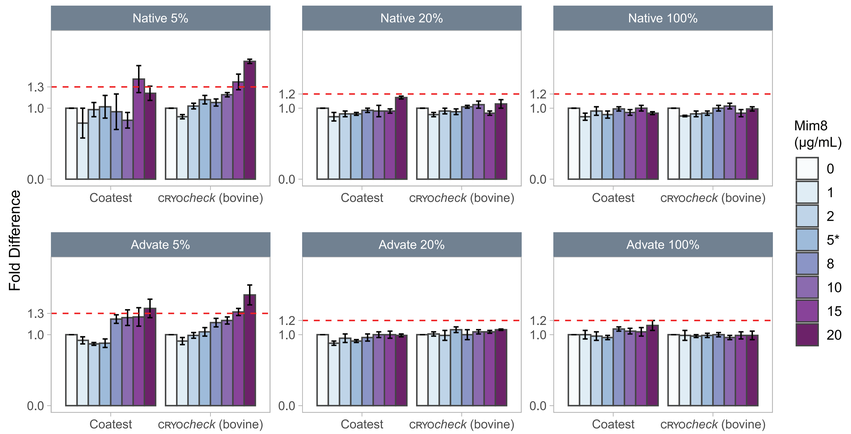

Table 1

Maximum Allowable Concentration of Mim8 from Dose Response Testing.

The assay, sample and the maximum allowable interferent dose (µg/mL) without interference (where the 95% confidence interval of the slope did not cross the maximum allowable difference) are presented.

Target FVIII Level	Sample Type	Mim8 Dose (µg/mL) without Interference		
		Biophen FVIII:C	Coatest SP4 FVIII	CRYO*check* Chromogenic Factor VIII (bovine)
100%	Native	0	20	20
	Advate	0	20	20
20%	Native	0	20	20
	Advate	0	20	20
5%	Native	0	10.3	9.2
	Advate	0	12.3	10.8

References

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3. Matsushita et al. *Blood* 2024;144(1):718–719
4. Oldenburg et al. *N Engl J Med* 2017;377:809–818