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Monitoring of Emicizumab and Factor VIII Concentrate Interaction

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BACKGROUND

Emicizumab (emi) offers a new treatment approach for patients with hemophilia A (PWHA) with / without inhibitors. In perioperative - / emergency situations additional factor supplementation may be necessary on top of emi prophylactic therapy regime. A tailored therapy schedule targets maximum efficacy with minor increase of the thromboembolic risk. Both, factor concentrates (conc.) and emi lead finally to thrombin generation (TG). The in vitro study aims to answer the following questions using standardized Ceveron®TG Assay: (Q1) What effect do various factor VIII (FVIII) conc. exert on TG? (2) Do we observe similar effects of emi on TG as previously described? [1] (3) Is a relevant interaction between FVIII conc. and emi observable?

METHOD

Plasma from PWHA with (data not shown) and without inhibitors was used for spiking of emi and various FVIII concentrate.

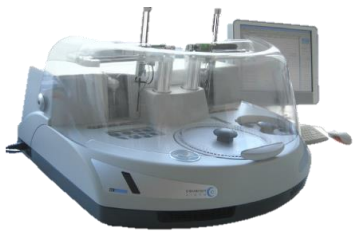

Fig.1 TG was determined fully automated under standardized conditions on the coagulation analyzer **Ceveron® α TGA** with Ceveron® TGA RB assay kit.

A calibration curve was made once at the beginning of the study using the standard analyzer settings for TGA calibration. nM Peak Thrombin values were used for result evaluation.

RESULTS

Under standardized conditions the potency in restoring TG in identical matrix is similar between the tested factor VIII compounds (> 150 nM at 0.1 IU/mL FVIII compared with < 25 nM in Haemophilia A patient samples). (Fig.2, L) Haemophilia A samples spiked with increasing concentrations of emi showed a continuous increase in peak thrombin over an extended concentration range, when TG was measured under standardized conditions. (Fig.2, R) Main results of spiking FVIII conc. on top of different emi conc. show a minor additive effect in low dose FVIII samples. Our data suggests that TG in the high FVIII content samples is triggered by FVIIIa alone (independent and non-additive of the presence of emi). (Fig.3 R/L)

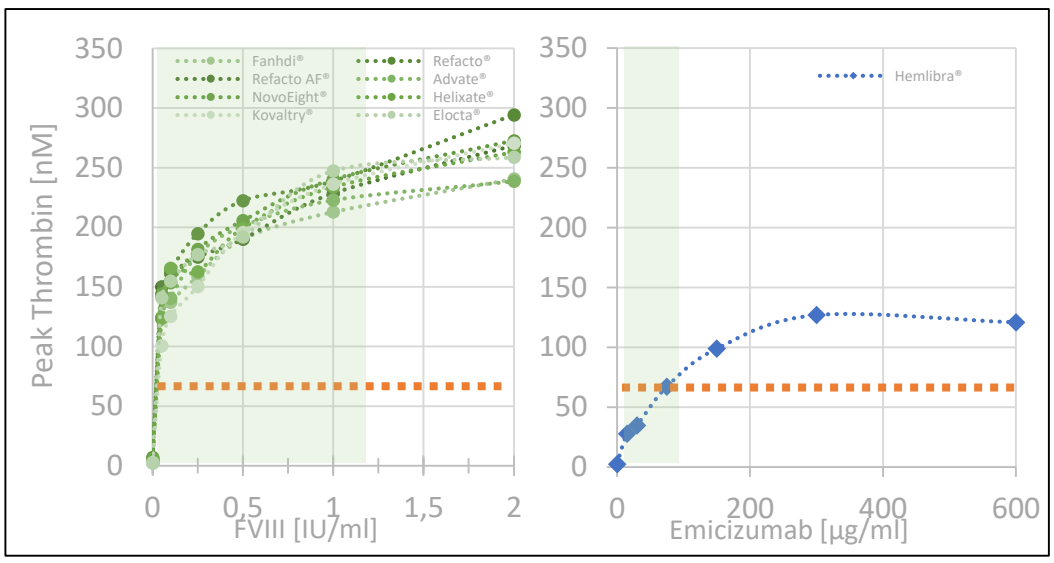

Fig.2: Effect of various FVIII conc. and emi on TG. Minimal amounts of FVIII conc. (0,05 IU/ml) lead to max. increase in thrombin, whereas additional FVIII results in much slower TG rate (above, R). TG induced by emi maxed at supra-physiological doses (green area = therapeutic range). In concordance with previously described data peak TG is about 30% compared to normal plasma (within therapeutic range) .[1]

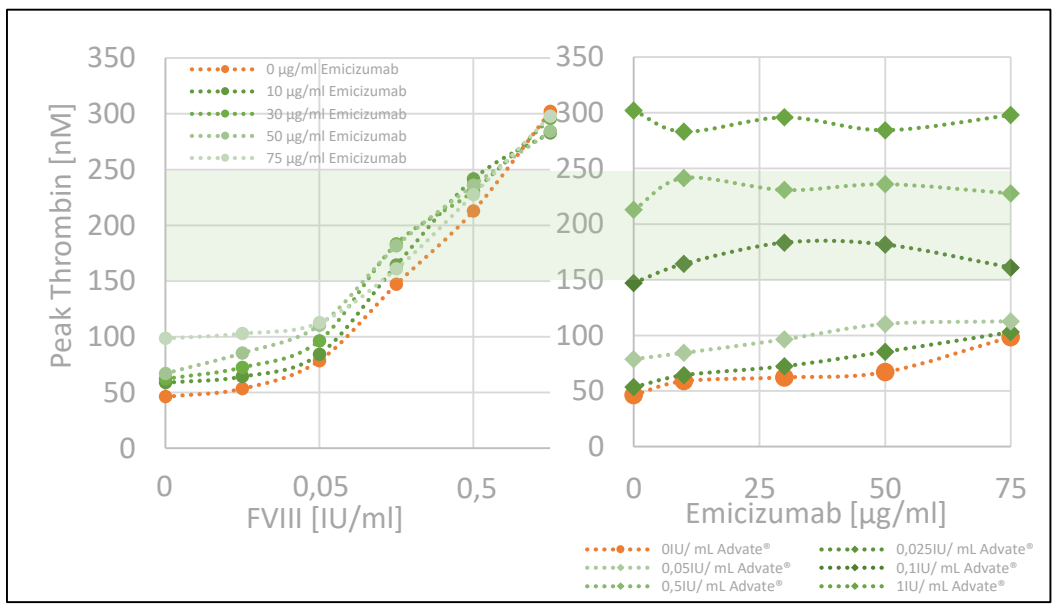

Fig.3: FVIII conc. on top of emi spiked in FVIII deficient plasma (0 BU): Effect on Peak Thrombin. Lower doses of a FVIII conc. (≤ 0,05 IU/ml) on top of emi exert a minor additional effect on TG. Clinically relevant FVIII doses (≥ 0,1 IU/ml) effect TG independently from the presence of emi.

CONCLUSION

The type of FVIII conc. has no relevant influence on TG assay and can be excluded as serious confounder (Q1). We do not observe *supra*-additive effects on TG when FVIII has been added on top of emi (Q3). TG measurement can serve as indicator for hemostatic balance (individualized therapy) in patients under prophylactic replacement therapy with emi and / or different FVIII conc., showing mainly the influence of FVIII conc. on TG.

[1] Schmitt C et al, EAHAD 2018