Combined FEIBA-FVIII therapy – a potential treatment for patients with hemophilia and inhibitors- a thrombin generation based study

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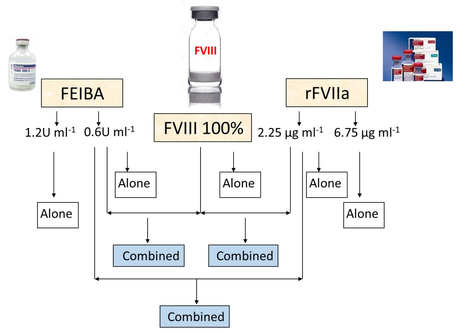
Background: Treatment of hemophilia A patients with inhibitors is challenging. Combined therapy with rFVIIa and FEIBA or rFVIIa and FVIII has previously been reported. However, no data is available regarding combined therapy with FVIII and FEIBA. Thrombin generation (TG) assay may serve as a tool for therapy tailoring.

Aim: We aimed to define patients' hemostatic response to single or combined concentrates by TG and asses their clinical response to pre-defined treatment.

Methods: Platelet-poor plasma from 15 severe hemophilia A patients with inhibitors was spiked with FVIII, rFVIIa and/or FEIBA. All TG matrices were assessed simultaneously. Based upon TG, an algorithm for individually-tailored therapy was suggested. Treatment, clinical and laboratory follow-up were documented.

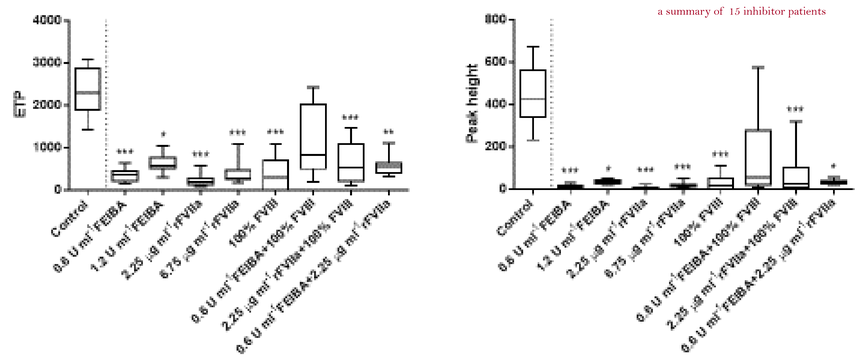
Ex vivo TG spiking matrix performed in all inhibitor patients plasma samples.



Ex-vivo spiking results:

- Individual TG responses were noted, without correlation to inhibitor titer.
- Combination of agents yielded augmentation of TG as compared to single agent.
- Although most patients had high responding (HR) inhibitors, additional FVIII spiking significantly augmented the TG induced by any bypass alone.
- Combined FEIBA+FVIII yielded the highest TG.

The effect of rFVIIa, FEIBA and FVIII alone or in combination on TG parameters compared to normal control - a summary of the inhibitor patients' cohort.



The data are presented as box-and-whiskers plots. The boxes span the 25th to the 75th percentile, the whiskers span the lowest to the highest observations, and the line inside each box denotes the median. The data were analyzed using Kruskal–Wallis test followed by Dunn's post hoc test (comparisons vs. Control). *P<0.05, **P<0.01, ***P<0.001.

Clinical Results: Based upon TG results, treatment was revised, and combined FVIII-FEIBA was administered to 7/15 patients, yielding a total of 396 episodes that were treated by combined therapy. Two children undergoing immune tolerance induction were switched to FEIBA-FVIII therapy, and one minor surgery (port-a-cath insertion) was performed. Most bleeding episodes responded to a single combined infusion. Neither thrombosis nor any other adverse events were documented.

Demographic data and characteristics patient cohort

Patient#	Age	BU	Mutation	ITI	Target joint	Bleeding frquency	Pre study Therapy	Comorbidity
1	1	4	deletion exon 8 + 9	yes	no	2-3/month	pdFVIII+rFVIIa	none
2	3.5	19	frameshift exon 14	yes	no	1/week	pdFVIII+rFVIIa	none
3	4	17	inv 22	yes	no	1-2/week	rFVIII+rFVIIa	none
4	4.5	8	none per exon seq	yes	no	1-2/ month	FVIII+rFVIIa	none
5	38	9	No inv	no	ankle, elbow ,knees	1/month	FEIBA	HCV
6	72	58	inv 22	no	knee,elbow	1/month	FEIBA	HCV
7	3	8	none per exon seq	yes	no	1-2/month	FVIII+rFVIIa	none
8	40	14	none per exon seq	no	elbow, knees	2-3/ month	FEIBA	HCV
9	6	12	NA	no	no	1/ month	FVIII+rFVIIa	none
10	6.5	9	inv 22	yes	no	1-2/ month	FVIII+rFVIIa	none
11	6	62	none per exon seq	yes	knee, ankle	2-3/ week	FVIII+rFVIIa	s/p ICH
12	50	34	No inv	no	knee elbow	1-2/month	FEIBA	HCV, IHD in family
13	30	620	del exon 13-21	failed	ankle, elbow	1-2/week	FEIBA+rFVIIa	HCV
14	1.5	64	inv 22	yes	no	2-3/month	FVIII+rFVIIa	none
15	25	11	none per exon seq	no	elbow	2-3/month	FEIBA	none

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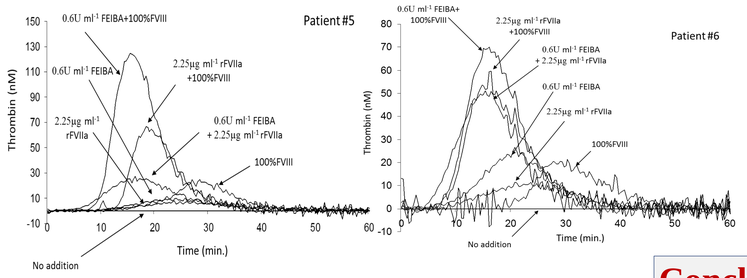
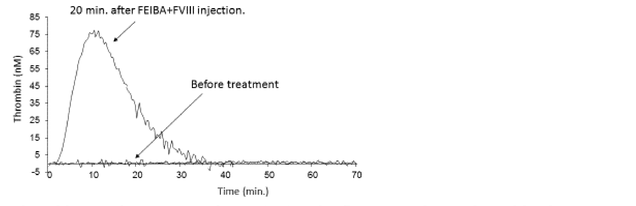
Representative TG curves of patient #5 and patient #6 PPP spiked with rFVIIa, FEIBA and FVIII alone or in combination.



A representative TG curve of patient #11 obtained before and 20 min after treatment with FEIBA (50 IU kg -1) and FVIII (70 IU kg -1).



TG was initiated by the addition of 1pM tissue factor (TF). The flat curve obtained in a bleeding patient prior to any treatment shows significant improvement once FEIBA and FVIII were administered.

Conclusions: Our study confirmed for the first time that the in vitro advantage of combining FVIII and FEIBA indeed accounts for improved hemostasis and may safely be applied to inhibitor patients.