Thrombin generation assay (TGA) for testing hemostatic response in patients with Hemophilia A and inhibitors on immune tolerance induction treatment (ITI): preliminary in vivo results from the PredicTGA study

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Topic: Inhibitors

OBJECTIVES

This prospective study was set up to evaluate whether TGA may predict hemostatic efficacy of different FVIII concentrate classes [full-length rFVIII (FLR), B-domain deleted rFVIII (BDDR) and plasma-derived FVIII/VWF (PD)] in patients with hemophilia (FVIII <2 IU/dl) and inhibitors receiving FVIII treatment. Baseline in vitro TGA and inhibitor cross-reactivity results from this study showed that PD was the least reactive against inhibitors and the most efficient in generating thrombin.

METHODS

Patients underwent a laboratory assessment after 72-h wash-out period followed by a prospective observation of 12 months (prophylaxis or on demand treatment) and a maximum of 33 months (ITI).

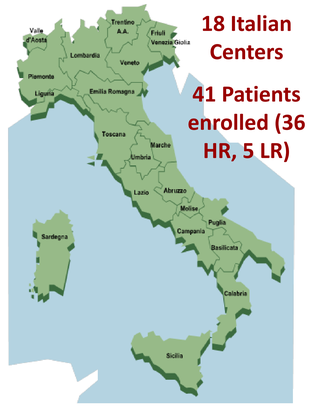

FIGURE 1 Recruitment details.

Centralized baseline laboratory assessment included in vitro spiking experiments mixing patient plasma with each of the 3 products at a concentration equivalent to FVIII doses used in clinical practice (50-200 IU/kg); TGA (CTA Thrombinoscope. Maastricht, NL) and inhibitor testing by Nijmegen-Bethesda assay were measured. FVIII and TGA before and after FVIII infusions were periodically repeated during follow-up(Figure 3).

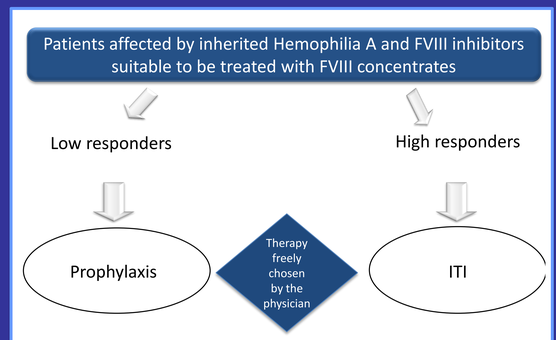

FIGURE 2 Study population: high responders (HR) and low responders (LR)

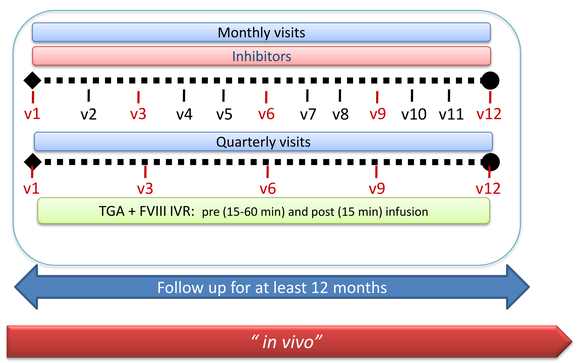

FIGURE 3 Study design

RESULTS

Twenty-three patients underwent the prospective phase; preliminary data from 12 (median age: 3.9 years; 1.2-63.3) who completed at least 12-month follow-up or terminated the observation period are reported. ITI started in 11 high responders (with PD in 6, FLR in 4 and BDD in 1) and prophylaxis with PD in 1 low responder. Post-infusion FVIII and peak thrombin values at first FVIII infusion (V1) according to FVIII dose and inhibitor titer are reported in Table 1. Post-infusion FVIII levels and peak thrombin values were correlated with inhibitor titer (r:-0.73, p=0.007 and r:-0.76, p=0.004, respectively) but not significantly with FVIII dose. Finally, a correlation was found between post-infusion peak thrombin and FVIII values (r: 0.61, p=0.034). Last update showed that, in addition to the 12 patients here reported, other 3 patients, who undewent ITI, reached at least the 12 months follow-up.

TABLE 1. Post-infusion FVIII and peak thrombin values at first FVIII infusion (V1) according to FVIII dose and inhibitor titer

Parameter	FVIII dose (IU/kg)	Inhibitor titer at V1		
		≤5 BU/ml	>5 BU/ml	Total
Number of patients	50-100	2	2	4
	150-200	2	6	8
	Total	**4**	**8**	**12**
Inhibitor titer at V1 BU/ml	5-100	3 (1-5)	9 (6-12)	6 (1-12)
	150-200	2 (0-3)	25 (7-1800)	15 (0-1800)
	Total	**2 (0-5)**	**15 (6-1800)**	**10 (0-1800)**
Post-infusion FVIII IU/dl	50-100	30 (25-34)	3 (0-5)	15 (0-34)
	150-200	288 (64-512)	11 (0-37)	15 (0-512)
Post-infusion peak thrombin nM.min	50-100	87 (45-130)	24 (13-35)	40 (13-130)
	150-200	183 (155-212)	25 (7-30)	30 (7-212)

CONCLUSIONS

TGA showed to be sensitive in distinguishing different responses in inhibitor patients undergoing FVIII replacement. Analyses are underway in all the patients undergoing the follow-up phase to assess the correlation of baseline in vitro data with laboratory results obtained in vivo, the hemostatic response to FVIII and ITI outcome.

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