A novel, prospective study reveals the benefit of peak factor VIII protection from the patient's perspective

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INTRODUCTION

- Severe hemophilia A patients have <1% Factor VIII (FVIII) levels
- The goal of prophylaxis has traditionally been to maintain patients above a certain FVIII trough level, typically 1%.
- A recent study demonstrated that higher FVIII peak levels and more time spent above 20% and 30% FVIII levels are associated with fewer bleeding episodes in severe haemophilia A.[1]
- These higher levels of FVIII are typically realized only during the first 24 hours following infusion, a concept not understood by all patients.
- To our knowledge, no patient research has been conducted to assess the relationship between time since last FVIII infusion and how protected from bleeding the patient feels.

OBJECTIVE

- Primary Objective: Assess the relationship between the time since the last FVIII infusion and how protected from bleeding the patient feels.
- Secondary Objective: Quantify patient perception of the role of factor within their body and what this means to them.

METHODS

Study Overview

- A prospective, non-controlled, week-long observational study was conducted in the US.
- Institutional Review Board (IRB) approval and informed consent were obtained.

Study Subjects

- Subjects who met all of the following criteria were eligible for the study:
  - Diagnosed with severe Hemophilia A (<1% FVIII levels)
  - 18 years or older
  - Prescribed FVIII prophylaxis
- Subjects who met any of the following criteria were not eligible for study:
  - Subject has a current inhibitor
  - Subject is unable to read or understand English
  - Subject does not have a cell phone that can send and receive text messages

Subject Recruitment

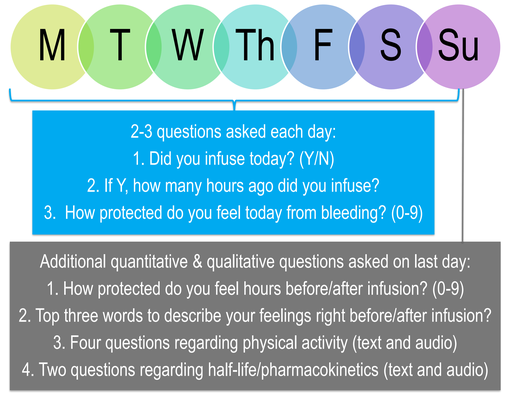
- Sample size target was 100 patients.
- Study subjects were recruited from inVibe's hemophilia A patient panel.
- All members of the panel were sent an email inviting them to participate in the study.
- The email included a link to a website where patients were provided more information regarding the study and were asked a number of questions to determine if they met inclusion and exclusion criteria.
- Those who met the criteria were asked to call the primary investigator if they had any questions about the study.
- Study subjects provided informed consent electronically.
- Once enrolled, study subjects were asked to provide the following demographic information:
  - FVIII product and prescription
  - Patient weight
  - Highest education level
  - If they visit an HTC at least once per year
  - Cell phone number to participate in the daily text messages

METHODS

Study Design

- The day following enrollment was considered Day 1 of the study.
- Study subjects received daily text messages asking them if they infused, and if so, how many hours ago, and how protected from bleeding they felt on a scale from 0-9, where 0=not protected at all and 9=extremely protected.
- On the final day, subjects completed additional quantitative and qualitative questions via text & an automated phone survey, respectively.
- Daily text messages were sent at 9am local time for the study subject. If a study subject did not answer that SMS, a reminder was sent at 12 noon and again at 6pm, if necessary. If they did not complete the daily survey by midnight, their participation in the study was terminated.
- On days when the study subject indicated that they had infused, they were sent an additional question 3, 7 and 11 hours afterwards to determine how protected they felt from bleeding (on a scale from 0-9).
- Subjects received honoraria for each day of participation.

Figure 1: Study Design Schematic for a Patient Starting on a Monday



Statistical Methods

- All subject data (including phone numbers) were de-identified for analysis.
- Audio responses were transcribed for analysis.
- Descriptive statistics were used to describe the study population.
- Subjects prescribed an extended half-life (EHL) rFVIII were separated from those prescribed standard FVIII (plasma-derived or recombinant) given that ratings of protection may be influenced by FVIII product type.
- Summary statistics were used to explore the relationship between infusion and level of perceived protection from bleeding.
- A mixed model for repeated measures with autoregressive heterogeneous variances was utilized to determine what variables were significantly associated with feeling protected within 4 days after infusion.
- The regression analysis controlled for FVIII type, age and dose per kg.
- Word clouds were created to represent the frequency of the top words used to describe their feelings right before and after infusion.

RESULTS

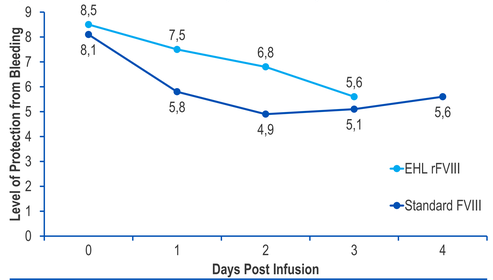
Sample Size & Subject Demographics

- Of 132 subjects enrolled, 1 dropped out on Day 7, 6 did not complete the audio response questions on Day 7, and 3 were excluded due to inconsistent demographic data.
- 121 (92%) subjects were included in the final analysis dataset.
- The average subject was 29 years old, weighed 88 kg and reported a prescribed a dose of 41IU/kg.
- The most common product and infusion schedule were ADVATE and 3x/week (47.1% and 45.5% of the sample, respectively).
- 104 (86.0%) and 17 (14.0%) subjects reported using standard FVIII and EHL rFVIII, respectively.

Infusions & Feelings of Protection

- Un-adjusted mean ratings of protection by day since last infusion are provided in Figure 1 and the number of observations for each are below.
- Because there were only 3 observations for 5-days post infusion, these were excluded from Figure 1 and the regression analyses.

Figure 1: Protection Scores by Product Type & Day Post Infusion



Number of Observations	17	17	15	8	0
	104	98	71	21	9

Regression Analyses (Table 2)

- Subject-reported protection scores decreased each subsequent day following infusion (all p<0.0001) after controlling for FVIII type, age and dose.
- Adjusted protection scores for the infusion day and each subsequent day were 8.2, 6.1, 5.2, 4.5 and 4.3, respectively.
- This corresponded to a 25.9%, 13.7%, 13.7% and 4.5% decreased feeling of protection on days 1, 2, 3 and 4 compared with the day before.

Table 2: Regression Analysis of Protection Scores by Day Post Infusion, FVIII Type, Age and Dose

Variable		Estimate	Std Error	P-Value
Intercept		8.06	0.45	**<0.0001**
Day Post Infusion	1 vs. 0	-2.12	0.16	**<0.0001**
	2 vs. 0	-2.95	0.19	**<0.0001**
	3 vs. 0	-3.66	0.32	**<0.0001**
	4 vs. 0	-3.87	0.69	**<0.0001**
FVIII Type	EHL vs Standard	0.53	0.27	0.0536
Age		0.005	0.01	0.644
Dose per Kg		-0.003	0.007	0.703

Figure 2: Top 10 Words Used to Describe Feelings Right Before Infusion (Corresponding to FVIII Trough Levels)

Descriptor	N	%
Anxious	34	10.4%
Worried	24	7.3%
Nervous	23	7.0%
Unprotected	18	5.5%
Pain	11	3.4%
Sore	11	3.4%
Scared	8	2.5%
Unsafe	8	2.5%
Weak	6	1.8%
Stressed	5	1.5%
Vulnerable	5	1.5%

Figure 3: Top 10 Words Used to Describe Feelings Right After Infusion (Corresponding to FVIII Peak Levels)

Descriptor	N	%
Safe	51	15.5%
Protected	47	14.2%
Relieved	23	7.0%
Happy	17	5.2%
Confident	11	3.3%
Healthy	11	3.3%
Comfortable	10	3.0%
Normal	10	3.0%
Secure	10	3.0%
Satisfied	9	2.7%

DISCUSSION

- This research uncovered that subjects receiving factor replacement therapy felt significantly more protected when at higher FVIII levels in the first 24 hours post infusion.
- Given the recent finding that higher FVIII peak levels are associated with fewer bleeding episodes,[1] future research should explore how FVIII levels might influence patient perception of bleeding protection.
- We encourage additional research to further understand the benefits of high FVIII levels and which patients benefit most from these FVIII levels.

CONCLUSION

- Patients reported feeling very protected from bleeding the day they infused FVIII, with the first day following infusion demonstrating the biggest drop in perceived protection.
- This suggests that patients receiving factor replacement therapy perceive a real benefit of FVIII peak levels achieved on the day of infusion.

REFERENCES

1. Valentino LA, Pipe SW, Collins PW, et al. Association of peak factor VIII levels and area under the curve with bleeding in patients with haemophilia A on every third day pharmacokinetic-guided prophylaxis. Haemophilia 2016 Mar 1. doi: 10.1111/hae.12905.

DISCLOSURES

*Jason Booth and Sheetal Patel are employees of Baxalta (Baxalta US Inc), now part of Shire. The studies were sponsored by Baxalta US Inc., now part of Shire.