Recurrence of Inhibitors After Immune Tolerance Induction: A Retrospective Single-Center Study

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Introduction

Development of neutralizing anti-Factor VIII (FVIII) antibodies is the most common complication in persons with hemophilia-A (PWHA) using exogenous factor products [1]. Age of exposure, hemophilia type, genetic mutation and type of factor (plasma derived or recombinant) treatment have been reported to play a role in immunogenicity [2]. Immune Tolerance Induction (ITI) can achieve antigen-specific tolerance using high dose FVIII to eradicate the inhibitor [3]. PWHA with no anamnestic response can continue to use FVIII products. With the development of long-acting FVIII proteins, PWHA will have the option to use these products. However, prior inhibitor formation in PWHA is an exclusion criterion of clinical trials with extended half-life FVIII products. Therefore, no data exist on the recurrence of FVIII inhibitor after exposure to long-acting FVIII products.

Objective

To conduct a retrospective analysis on the recurrence of alloantibodies to FVIII in PWHA with a history of inhibitor formation who completed ITI and continued using recombinant FVIII products after successful ITI.

Methodology

With Institutional Review Board approval, medical records from the Hemophilia Treatment Center database were analyzed to identify patients with FVIII deficiency <2 %, a history of alloantibodies to FVIII who had undergone successful ITI. ITI success was demonstrated by either a normal FVIII half-life or undetectable inhibitor titer. Select demographic, therapeutic and comorbid parameters were analyzed. (see table)

Results

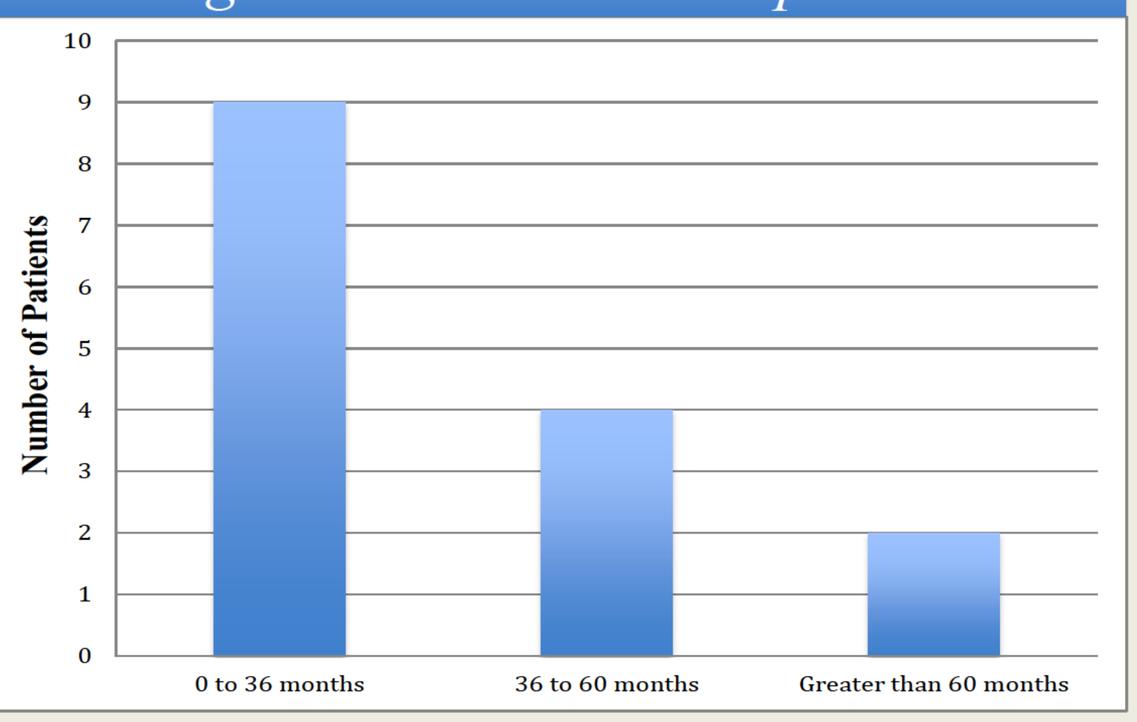
Fifteen patients (fourteen with FVIII <1% and one with FVIII 1%) with inhibitors to FVIII and who successfully underwent ITI were identified. The mean age at inhibitor detection was 39 months with a median of 18 ½ months. Prior to ITI, twelve patients had measurable inhibitor titers greater than five Bethesda units (BU), two patients had less than five BU and one patient had unknown titers (ITI begun elsewhere). All patients continued using FVIII products after successful ITI. None of the patients developed a recurrence of the inhibitor after continued use of either plasma derived or recombinant FVIII products. No patient discontinued factor prophylaxis and initiated on-demand therapy. One patient is lost to follow-up. Because there were no recurrences, no predictive factors could be identified. The estimated inhibitor recurrence risk is ≤ 20% ($p<0.05$).

Experience With ITI

Patient #	BU Titers	Factor used Prior to Inhibitor*	ITI Regimen	Current Prophylaxis	Current Factor product	Ethnicity
1	960	Recombinant	200 IU/KG BID	QOD	Recombinant	Caucasian
2	48	Recombinant	200 IU/KG QD	TIW	Recombinant	Hispanic
3	6.8	Recombinant	100 IU/KG QD	TIW	Plasma-Derived	African American
4	7.6	Recombinant	100 IU/KG QD	TIW	Recombinant	Caucasian
5	40	Plasma-Derived	200 IU/KG QD	QOD	Recombinant	American Indian
6	0.9	Recombinant	100 IU/KG QD	QOD	Recombinant	Hispanic
7	63	Plasma-Derived	100 IU/KG QD	QOD	Recombinant	Hispanic
8	4	Recombinant	200 IU/KG QD	TIW	Recombinant	African American
9	18	Plasma derived	50 IU/KG QD	UNK	Plasma Derived	Caucasian
10	13.5	Recombinant	100 IU/KG QOD	QOD	Recombinant	Caucasian
11	224	Plasma Derived	200 IU/KG QD	QD	Plasma Derived	East Asian
12	17	Plasma Derived	200 IU/KG QD	BIW	Recombinant	Caucasian
13	unk	Recombinant	100 IU/KG QD	BIW	Recombinant	Caucasian
14	7.2	Recombinant	50 IU/KG QD	QOD	Recombinant	Caucasian
15	19	Recombinant	50 IU/KG QD	BIW	Recombinant	Caucasian

*Factor used prior to inhibitor

Age at Inhibitor Development



Conclusions

After successful ITI:

- Patients have a low risk of inhibitor recurrence
- Type of FVIII product prior to, or after ITI did not influence inhibitor recurrence

The small numbers in this study preclude accurate estimation of recurrence risk. Because no patient discontinued prophylaxis, recurrence risk with on-demand therapy is unknown. Further studies with more patients would permit better estimates of recurrence risk.

Prediction to Test

Since the protein structure of long-acting FVIII is identical to current FVIII products, it is reasonable to expect that after successful ITI, patients who remain on factor prophylaxis will not experience inhibitor recurrence after exposure to long-acting FVIII products.

References

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