Prophylaxis with three days per week FEIBA is effective hemostasis in young children with Hemophilia A with inhibitors

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Conclusions

1. **FEIBA prophylaxis, 75-100 units/kg, given 3 days per week, is a well tolerated regimen in young children (< 3 years old) with Hemophilia A with inhibitors**
   - Safe and effective in most children with minimal breakthrough bleeding and minimal adverse effects
   - Some patients experienced a rise in inhibitor titre but this was transient and did not result in discontinuation of FEIBA

2. **In addition to providing effective prophylaxis for children not receiving immune tolerance induction (ITI), this regimen was also effective prophylaxis during immune tolerance induction**
   - Allows for better balance between effective prevention of bleeding and treatment and cost burden when using multiple factor products
   - Further validation would require a study with direct comparison to higher dose FEIBA prophylaxis regimens during ITI

Introduction

- Neutralizing antibodies to factor VIII occur in 30% of children with Hemophilia A.
- Prophylaxis with FEIBA 75-100 units/kg every other day has been shown to be effective prophylaxis in patients with Hemophilia with inhibitors who have failed ITI or who are unable to receive ITI.[1,2]
- These studies were conducted in older children (>3 years old)[1,2] while other studies used higher dose regimens.[3]
- In children receiving concomitant ITI, previous studies have used higher dose regimens of daily to twice daily FEIBA with concomitant ITI[4,5] but data in children <6 years of age is limited.
- These approaches have significant drawbacks including a high treatment burden on the patient; need frequent central line access and enormous cost to the patient and medical system.

Aim

We sought to achieve a better balance between treatment burden and cost with maintaining good prevention of bleeding by using FEIBA prophylaxis only three times a week whether the patient is receiving ITI or not.

Methods

- The medical records of 10 children with severe Hemophilia A with inhibitors were reviewed.
- Six children were part of a previous review[6] and their records were re-analyzed.
- All children received FEIBA prophylaxis, 75-100 units/kg, 3 days per week as part of their inhibitor management.
- FEIBA prophylaxis was started at inhibitor detection and continued through the start of ITI until the inhibitor titre dropped below 2 Bethesda units/mL (BU/mL).

Results

Table 1. Outcome while on FEIBA Prophylaxis

Patient	Gene Mutation	Exposure Days	Titre at Diagnosis	Peak Titre	Bleeding Episodes	Rise in Titre?	Concomitant ITI	Reason for FEIBA Discontinuation	Duration on FEIBA (months)	Overall Outcome
1	Inversion intron 22	31	134.4	248.3	6	No	No	Switch to rFVIIa due to better bleed response despite decrease in titre	77	Ongoing ITI with plasma-derived factor VIII
2	Inversion intron 1	19	49.9	88.4	2	1	4 months	Decrease in titre on ITI	54	Ongoing ITI with plasma-derived factor VIII
3	Exon 18	30	16.7	16.7	0	No	No	Anaphylaxis to FEIBA	16	ITI failure with plasma-derived FVIII, now on rFVIIa prophylaxis
4	Inversion intron 22	26	1.0	1.0	0	No	No	Decrease in titre to 0 BU/mL, able to start ITI	1	Successful ITI, on regular FVIII prophylaxis
5	Inversion intron 22	14	105.0	105.0	7	2	15 months, 1st ITI 8 months, 2nd ITI	Decrease in titre to 0 BU/mL with 2nd ITI	84	ITI failure on low-dose I-ITI arm; ongoing ITI with plasma-derived factor VIII
6	Inversion intron 22	20	28.8	28.8	0	No	No	Decrease in titre to <2 BU/mL, able to start ITI	12	Successful ITI, on regular FVIII prophylaxis
7	Inversion intron 22	2	15.8	24.6	1	1	12 months	Decrease in titre to 0 BU/mL with ITI	28	Successful ITI, on regular FVIII prophylaxis
8	Unknown	96	15.5	15.5	1	No	No	Decrease in titre to <2 BU/mL, able to start ITI	13	Started ITI, moved to another treatment centre, outcome unknown
9	Unknown	27	7.6	7.6	0	No	No	Decrease in titre to <2 BU/mL, able to start ITI	6	Successful ITI, on regular FVIII prophylaxis
10	Exon 7	67	19.8	19.8	0	No	8 months	Decrease in titre to 0 BU/mL with ITI	20	Successful ITI, on regular FVIII prophylaxis

- Inhibitors developed before 100 exposure days (ED) in all patients, before 50 ED in 8/10 (Table 1 & 2).
- All children were under 36 months of age at inhibitor onset and onset of FEIBA prophylaxis (Table 2).
- All 10 children had decrease in inhibitor titre while on FEIBA.
  - 3 had 4 transient increases in titres related to infection (pt. 5, 7), ITI failure (pt. 5), and unknown (pt. 2)(Figure 1).
- Three children had repeated bleeding while on FEIBA prophylaxis despite decreasing titre (patients 1,2,5); bleeding improved with switch to rFVIIa and ITI start (pt. 1) or with starting ITI (pts. 2, 5) (Table 1).
- Patient 3 developed anaphylaxis after 4 months on FEIBA prophylaxis. His titre still decreased in that time period.
- 7 children had 0 - 1 bleeding episodes during FEIBA prophylaxis
- There were no thrombotic episodes.
- 8/10 children safely remained on FEIBA prophylaxis for over 1 year (Table 1, Figure 1).
- 4 children were on concomitant ITI and FEIBA and had no significant bleeding (Table 1).

Figure 1. Timeline and progress of patients 2 (left) and 5 (right) while on FEIBA prophylaxis

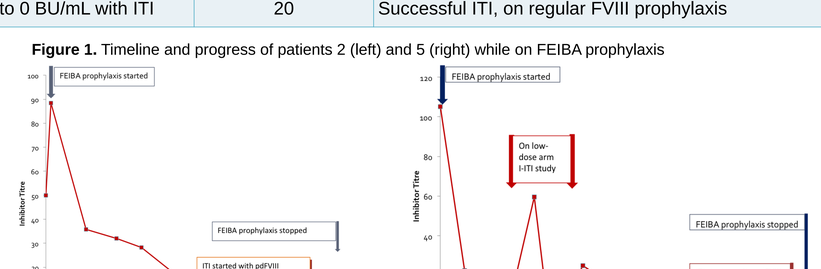

Table 2. Summary of inhibitor onset and treatment

Age at Inhibitor Detection (months)	
Mean Median (Range)	16 14 (9 – 36)
Cumulative Exposure Days before Inhibitor Onset	
Mean Median (Range)	33.2 26.5 (2 – 96)
Age at Start of FEIBA Prophylaxis (months)	
Mean Median (Range)	18 15.5 (10 – 36)
Duration of FEIBA Prophylaxis (months)	
Mean Median (Range)	24.7 13 (1 – 84)

References
1. Leissinger et. al. N Engl J Med 2011; 365:1684-1692.
2. Antunes et al. Haemophilia 2014; 20:65-72.
3. Perry et. al. Haemophilia 2010; 16:80-89.
4. Kreuz et. al. Ann Hematol 2001; 80:138a.
5. Valentino. Haemophilia 2009; 15:733-742.
6. McClure et al. Haemophilia 2010; 16(Suppl 4):75.

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