Transition to Fc-fusion recombinant factor VIII using a pediatric pharmacokinetic based protocol: Real life individualized prophylaxis

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Objective

To describe our pediatric experience with individualized factor prophylaxis when transitioning from standard half life factor VIII product to Fc-fusion recombinant factor VIII using a pharmacokinetics (PK) based protocol.

Introduction

- In 2014, the US FDA approved Fc-fusion recombinant factor VIII (Fc-rFVIII) for adult and pediatric hemophilia A patients
- The recommended prophylaxis dosing of Fc-rVIII is 50u/kg every 4 days. Doses and frequency may be adjusted based on response. For children less than 6 years old, more frequent or higher doses of up to 80u/kg may be needed.
- Children's Minnesota HTC developed a protocol to assess pharmacokinetics for all pediatric hemophilia A patients who transitioned to Fc-rVIII for prophylaxis

Methods

- All children at our institution with severe hemophilia A, who transitioned to prophylaxis with Fc-rVIII, were initially prescribed 50-80 u/kg (+/- 10%) every 4 days.
- Factor VIII levels were requested at multiple times points (+/- 12 hours) following infusions of Fc-rVIII: 24, 48, 72 and 96 hours post infusion.
- When factor VIII levels were not obtained at the requested time points, assumptions were made based on documented levels. If a level was ≥1%, all earlier time points were assumed as >1%. If a level was 1%, all subsequent time points were assumed as <1%.
- Dose changes were recommended per provider discretion based on PK, patient activity level and break through bleeding
- A retrospective chart review of all patients at our institution treated with Fc-rVIII was completed

Results

- Fourteen pediatric hemophilia A patients (ages 3-18 years) transitioned to Fc-rVIII with a median follow up of 15.5 months (range 5-17 months)
- Initial median dose prescribed was 51.5 u/kg (range 35-80u/kg) every 4 days
- Five patients, 36%, required dose escalations above the recommended 50u/kg (+/- 10%) due to 72 hour trough factor VIII level being ≤2%. One patient initially started on a lower dose because the patient had historically required lower doses of standard half life recombinant factor VIII, this patient required dose escalation from 35u/kg to 52u/kg.
- Final median dose prescribed for all patients was 52.5 u/kg (range 41-98 u/kg)
- However, final median dose for those <6 years old was 83u/kg, 6-11 year olds was 52u/kg, 12-18 year olds was 51u/kg
- Final frequency was every 3 days in 4 patients, every 4 days in 5 patients, twice weekly in 4 patients and once a week in 1 patient
- At final doses, all patients had measurable levels at 48 hours post infusion. 90% of patients had a measurable level at 72 hours post infusion. 55% of patients had a measurable level at 96 hours.

Table 1: Percentage of Factor VIII levels ≥ 1%

Age Groups		24 hours	48 hours	72 hours	96 hours
< 6 years (n=3)					
	Initial Dose	100% (2/2)	100% (2/2)	33% (1/3)	0% (0/3)
	Final Dose	100% (3/3)	100% (3/3)	67% (2/3)	67% (2/3)
6-11 years (n=5)					
	Initial Dose	100% (4/4)	100% (2/2)	50% (2/4)	33% (1/3)
	Final Dose	100% (4/4)	100% (3/3)	100% (3/3)	33% (1/3)
12-18 years (n=6)					
	Initial Dose	100% (6/6)	100% (5/5)	100% (5/5)	66% (2/3)
	Final Dose	100% (5/5)	100% (4/4)	100% (4/4)	66% (2/3)
All patients (n=14)					
	Initial Dose	100% (12/12)	100% (9/9)	66% (8/12)	33% (3/9)
	Final Dose	100% (12/12)	100% (10/10)	90% (9/10)	55% (5/9)

Table 2: Patient Characteristics

Patient	Age at transition (years)	Baseline factor VIII level	Initial Dose (units/kg)	Final Dose (units/kg)	Duration of follow-up (months)	Frequency of infusions
1	3	<1%	56	83	17	Twice a week
2	4	<1%	75	98	16	Twice a week
3	5	<1%	80	80	11	Every 3 days
4	6	<1%	68	90	17	Every 3 days
5	7	<1%	52	52	16	Twice a week
6	10	<1%	35	52	10	Every 4 days
7	10	<1%	48	48	13	Every 4 days
8	10	<1%	41	41	14	Every 3 days
9	12	<1%	51	77	17	Twice a week
10	13	<1%	55	55	17	Once a week
11	15	<1%	53	53	15	Every 4 days
12	16	<1%	48	48	16	Every 4 days
13	16	<1%	43	43	5	Every 3 days
14	18	<1%	45	45	5	Every 4 days
Median	10	<1%	51.5 u/kg	52.5 u/kg	15.5	Unable to calculate

Conclusions

- Obtaining multiple PK data points in pediatric patients transitioning to Fc-rFVIII is useful to confirm prophylactic dosing schedule
- These data suggest pediatric patients > age 6 should start at the recommended dosing of 50 u/kg of Fc-rVIII.
- These data suggest considering starting pediatric patients ≤6 year olds near 80u/kg Fc-rVIII
- Adjusting the dose based PK data was valuable in order to obtain a measurable factor VIII trough level at 72-96 hours post infusion.
- 90% of patients had a measurable factor VIII level at 72 hours following individualized dose adjustments. These data suggest every three day dosing of Fc-rVIII for pediatric patients would be most appropriate based on PK data. 55% had measurable levels at 96 hours and could be dosed twice a week.

References

1. Mahlangu J, Powell JS, Ragni MV, et al; A-LONG investigators. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood*. 2014;123(3):317-325.
2. Eloctate ®(package insert). Cambridge, MA: Biogen; 2016.