Transition to FC-Fusion recombinant factor IX 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 IX product to Fc-fusion recombinant factor IX (Fc-rFIX) using a pharmacokinetics (PK) based protocol.

Introduction

- In 2014, the US FDA approved Fc-fusion recombinant factor IX (Fc-rFIX) for adult and pediatric hemophilia B patients
- The recommended prophylaxis dosing of Fc-rFIX is 50u/kg every 7 days or 100u/kg every 10 days, with dosing adjustments based on individual response
- Children's Minnesota HTC developed a protocol to assess pharmacokinetics for all pediatric hemophilia B patients who transitioned to Fc-rFIX for prophylaxis

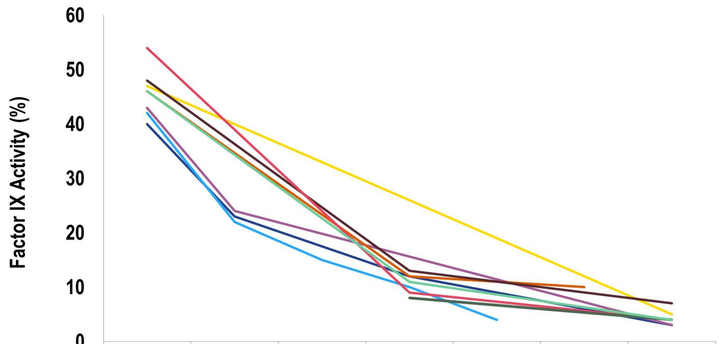
Methods

- All children at our institution with moderate or severe hemophilia B who transitioned to prophylaxis with Fc-rFIX were initially prescribed 50u/kg (+/- 10%) once a week
- Factor IX levels were initially requested at three time points following infusion of Fc-rFIX: 30 minutes, 72 hours and 168 hours post infusion. Later, additional time points (24 and 48 hours post infusion) were added to help guide prophylaxis and bleeding treatment.
- 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-rFIX was completed

Results

- Eight pediatric hemophilia B patients (ages 7-19 years) transitioned to Fc-rFIX with a median follow up 11 months (range 6-18 months)
- A median of 3 factor IX PK data points were obtained. The range was 2-5 (see Table 1)
- Four patients, 50%, were maintained on the originally prescribed dose of 50u/kg once every 7 days
- Four patients required dose modification. Patient 1 and 5 required dose escalation up to 72-88u/kg once every 7 days, secondary to a historically documented need for a trough of 5% and increased pain on the last several days prior to infusion, respectively. Patient 2 requested interim FIX dosing due to his active lifestyle. Patient 7 decreased his dose to 41u/kg once every 7 days to use a single vial for infusions.
- Patients 2, 3, 6 and 7 had breakthrough bleeding (see Table 2).

Table 1: Individual PK Data on Initial Fc-rFIX Dosing



	30 min	24 hr	Day 2	Day 3	Day 5	Day 6	Day 7
Patient 1	40	23		12			3
Patient 2	42	22	15	10	4		
Patient 3	43	24					3
Patient 4	46			12		10	
Patient 5	47						5
Patient 6	48			13			7
Patient 7	54			9			4
Patient 8				8			4
Median	46			11			4

Table 2: Patient Characteristics

Patient	Age at transition (years)	Baseline factor IX level	Initial Dose (units/kg)	Final Dose (units/kg)	Duration of follow-up	Bleeds?
1	10	1%	48	72	11 months	none
2	10	<1%	45	45***	22 months	On 4 occasions required dosing a day early for concerns of right ankle bleed (pain/swelling)
3	16	2%*	52	52	11 months	Required factor for a right shoulder when factor was held for a comp clinic
4	7	<1%	48	48	6 months	none
5	7	2%**	44	88	9 months	none
6	11	2%	45	45	10 months	1 muscle bleed related to baseball, 2 days following prophylactic dose
7	17	<1%	55	41	18 months	6 bleeds related to trauma, all resolved in 1 dose, patient was non-compliant with prophylactic dosing and treating on demand during this time
8	19	<1%	54	54	15 months	none
Median	10.5		48	50	11 months	Not applicable

* heterozygote factor VII deficiency **Mild von Willebrands ***Added interim FIX dosing

Conclusions

Obtaining multiple PK data points in the pediatric patient transitioning to Fc-rFIX was feasible and useful to confirm prophylactic dosing, estimate appropriate bleed dose and to have a meaningful discussion with the family regarding individualization of factor administration.

References

1. Powell JS, Pasi KJ, Ragni MV, et al; B-LONG Investigators. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. N Engl J Med . 2013;369(24):2313-2323.
2. Alprolix ® (package insert). Cambridge, MA: Biogen; 2016.