Advancing Treatment for Hemophilia B

Exploring Extravascular Hemostasis and Optimizing Factor Replacement Monitoring and Implementation

Hemophilia B: Introduction

- Hemophilia B is caused by a deficiency in FIX—a hemostatic enzyme—and affects 3.8 per 100,000 males
- FIX deficiency prevents the propagation phase of hemostasis, precluding the synthesis of sufficient amounts of fibrin

HEALTHY HEMOSTASIS

HEMOPHILIA B

Figure courtesy of Dr. Guy Young

FIX Distribution and PK: Differences From HFVIII

- Differences between FIX (hemophilia B) and FVIII (hemophilia A) result in distinct distribution and PK profiles
- Unlike FVIII, FIX rapidly migrates outside of the vasculature and is present in both the intravascular and extravascular compartments
  - —Intravascular compartment as a circulating protein
  - —Extravascular compartment bound to collagen IV
- Endothelial monolayer and basement membrane are enriched with collagen IV binding sites for FIX

HEMOPHILIA B – FIX

FIX shows a pronounced distribution to the extravascular space, potentially enabling a longer $t_{1/2}$

HEMOPHILIA A – FVIII

FVIII binds to VWF, largely limiting the distribution of FVIII within the bloodstream

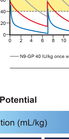
These different paths of distribution may have clinical importance

Affected PK Parameters	Unique Variables Influencing PK	
	FIX	FVIII
Half-life	• EVD • Collagen IV binding • 18-24 hours	• Blood type • VWF association • ≈12 hours
Volume of distribution	• EVD • Collagen IV binding • 220, 261 mL/kg (rFIX)	• VWF association • Interaction with clearance receptors • 50 mL/kg (rFVIII)
Clearance		• VWF association
Recovery	• EVD • Collagen IV binding	

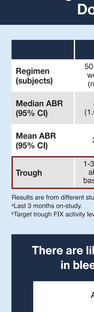
FIX and the 3-Compartment Model

FVIII and the 1-Compartment Model

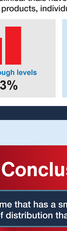
- Linear decay of a drug
- Concentration decreases by half over a constant period of time (eg, $t_{1/2}$)



FIX Therapies in the United States Vary in Structure, Characteristics, and PK Profiles



	rFIX-Fc	rFIX-FP	N9-GP	SHL-rFIX
Dose, IU/kg	50	50	40	50
AUC, IU·h/dL	3664	7176	14130	548
Clearance, mL/kg	0.74	0.77	0.42	8.62
Incremental recovery, IU/dL or IU/kg	0.92	1.27	2.00	0.084
$t_{1/2}$ for EHL product, mean	82.1	102.0	96.2	
$t_{1/2}$ extension relative to SHL-rFIX	2.4-fold	4.2-fold	4.8-fold	



Extravasation Potential

Volume of distribution (mL/kg)

N9-GP	rFIX-FP	rFIX	rFIX-Fc
47	102	261.1	314.8

Trough Levels Vary Across FIX Products and Do Not Correlate Well With ABR

	rFIX-Fc		rFIX-FP		N9-GP	
Regimen (subjects)	50 IU/kg weekly (n=61)	Interval-adjusted (n=26)	40 IU/kg weekly (n=40)	75 IU/kg bi-weekly (n=21)	10 IU/kg weekly (n=30)	40 IU/kg weekly (n=29)
Median ABR (95% CI)	3.0 (1.0-4.4)	1.4 (0.0-3.4)	0.0 (0.0-1.9)	1.1 (0.0-2.7)	2.9 (1.0-6.0)	1.0 (0.0-4.0)
Mean ABR (95% CI)	2.9[a]	2.0[a]	1.58 (1.02-2.44)	1.61 (0.93-2.80)	4.56 (3.01-6.90)	2.51 (1.42-4.43)
Trough	1-3 IU/dL above baseline[b]	1-3 IU/dL above baseline[b]	20 IU/dL (mean)	12 IU/dL (mean)	8.5 IU/dL (mean)	27.3 IU/dL (mean)

Results are from different studies and therefore inter-product comparisons cannot be made.
[a]Last 3 months on-study.
[b]Target trough FIX activity levels.

There are likely some modifiers and a potential role of EVD in bleeding control in patients with hemophilia B

Although clinical trials have not directly compared EHL-FIX products, individual trials have shown:

A broad range of trough levels
0.0%-27.3%

A narrow range of median bleed rates
0.0-2.95 ABR

Conclusions

FIX is an enzyme that has a smaller molecular size and a larger volume of distribution than FVIII, which is a co-factor

There is a lack of correlation between trough levels and bleed rates in hemophilia B

Treatment evaluation of EHL- and SHL-FIX replacement therapy should focus on outcomes rather than trough levels

Successful bleed prevention or control in severe hemophilia B may be predicted by:
- — Distribution of FIX in circulation and extravascular space
- — Presence of FIX in tissues at time of injury
- — CRM status may play role in response

References

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Abbreviations

ABR: annualized bleed rate
AUC: area under the curve
CRM: cross-reactive material
EGF: epidermal growth factor
EHL: extended half-life
EVD: extravascular distribution
FIX/FIXa: factor IX/activated FIX
FV/FVa: factor V/activated FV
FVIIa: factor VII/activated FVII
FVIII/FVIIIa: factor VIII/activated FVIII
FX/FXa: factor X/activated FX
N9-GP: nonacog beta pegol
PK: pharmacokinetics
rFIX-FP: recombinant FIX with human albumin
SHL: standard half-life
$t_{1/2}$: half-life
TF: tissue factor
TFPI: tissue factor pathway inhibitor
VWF: Von Willebrand factor