Association between FIX levels & bleeding rates in hemophilia B patients receiving rFIXFc or N9-GP

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Background

- Congenital hemophilia B is a rare bleeding caused by dysfunctional or absent blood clotting factor IX (FIX); it affects approximately 1 in 50,000 people in Canada, predominantly men.[1,2]
- Prophylactic infusion of FIX is essential for managing moderate-to-severe hemophilia B. Extended half-life (EHL) FIX concentrates, such as recombinant factor IX Fc fusion protein (rFIXFc) or nonacog beta pegol (N9-GP), have exhibited safety and efficacy in clinical trials and real-world settings.[3,4,5]
- Differences in the EHL pharmacokinetic (PK)/pharmacodynamic properties suggest that plasma FIX levels may not completely explain hemostatic control levels. rFIXFc, with a greater volume of distribution than N9-GP, transiently distributes into the extravascular space, whereas N9-GP remains largely confined to the intravascular compartment.[6,7,8]

Objective

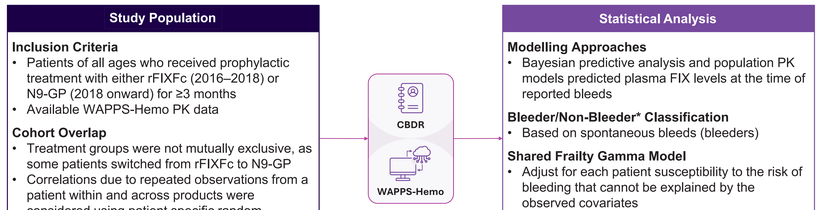
To explore the association between plasma FIX levels and bleeding rates in people with hemophilia B (PWHB) treated with rFIXFc or N9-GP.

Methods

Study design

- This study was a retrospective analysis of real-world patient data obtained from the Canadian Bleeding Disorders Registry (CBDR) and the Web-Accessible Pharmacokinetic Service-Hemophilia Service (WAPPS-Hemo) platform (**Figure 1**).

Figure 1. Study design



CBDR, Canadian Bleeding Disorders Registry; FIX, factor IX; N9-GP, nonacog beta pegol; PK, pharmacokinetic; rFIXFc, recombinant FIX fusion protein; WAPPS-Hemo, Web-Accessible Pharmacokinetic Service-Hemophilia Service platform.
*Non-bleeders are individuals who either carry the hemophilia gene without showing symptoms or have hemophilia but experience very few or no bleeding episodes due to mild disease or effective treatment.
**Discriminatory threshold analysis was performed using the highest predicted FIX level at the time of spontaneous bleeds (for bleeders) and the lowest observed trough level during prophylaxis (for non-bleeders).

Results

- Among the 210 PWHB, 72 were treated with rFIXFc and 67 with N9-GP; of these, population PK data were available for 33 and 34 patients, respectively.
- rFIXFc and N9-GP were administered once weekly at median doses of 60 and 41 IU/kg, respectively.
- Predicted FIX plasma levels at the time of spontaneous bleeding episodes for both bleeding and non-bleeding patients were higher for N9-GP than for rFIXFc (**Table 1** and **Table 2**).
- The percentage of spontaneous bleeding event is similar in both groups despite different predicted PK profile.

Table 1. Patient characteristics and bleeding summary among PWHB treated with rFIXFc or N9-GP

Parameter	rFIXFc	N9-GP
Overall characteristics		
No. of PWHB	33	34
Age (years), median (range)	17 (1–88)	42 (0.6–73)
Male, n (%)	33 (100)	34 (100)
BMI (kg/m^2), mean ± SD	24 ± 6	27 ± 5
Hemophilia severity*, n (%)		
Mild	1 (3)	0 (0)
Moderate	5 (15)	13 (38)
Severe	27 (82)	21 (62)
Bleed type summary		
Bleeder, n	24	25
Experienced spontaneous bleed while on treatment	14	18
Experienced traumatic bleed while on treatment	9	5
Spontaneous bleed only while receiving the other product	1	2
Non-bleeder, n	9	9

*Severe (FIX <1 IU/dL), moderate (FIX 1–5 IU/dL).
BMI, body mass index; FIX, factor IX; n, number of patients; N9-GP, nonacog beta pegol; PWHB, people with hemophilia B; rFIXFc, recombinant FIX fusion protein; SD, standard deviation.

Table 2. Predicted FIX at the time of a spontaneous bleed or trough at each infusion when there was no bleed among PWHB

Parameter	Spontaneous bleeders		Non-bleeders	
	rFIXFc	N9-GP	rFIXFc	N9-GP
No. of patients	14	18	9	9
No. of spontaneous bleeds	77	90	0	0
	For bleed treatments		When there was no bleed	
No. of infusions	77	90	709	534
	Predicted FIX (IU/dl) level at the time of spontaneous bleed		Through (IU/dl) at each infusion when there was no bleed	
Mean ± SD	16 ± 14	45 ± 26	16 ± 22	20 ± 17
Median (IQR)	13 (7, 20)	38 (26, 58)	7 (3, 21)	14 (6, 29)
(min, max)	(1, 67)	(1, 132)	(1, 115)	(1, 96)

FIX, factor IX; IQR, interquartile range; N9-GP, nonacog beta pegol; PWHB, people with hemophilia B; rFIXFc, recombinant FIX fusion protein; SD, standard deviation.

- The association between FIX levels (per quartile) and bleeding episodes significantly varied between the two products (p=0.008 for interaction effect) (**Table 3**).
- For rFIXFc, spontaneous bleeding risk was lower in the 2nd and 3rd quartiles and higher in the 4th quartile than in the 1st quartile, indicated by a hazard ratio of <1. Nonetheless, these estimates were imprecise and statistically non-significant (**Table 3**).
- For N9-GP, spontaneous bleeding risk was higher in the 2nd, 3rd, and 4th quartiles than in the 1st quartile, indicated by a hazard ratio of >1. However, these estimates were highly imprecise and statistically non-significant (**Table 3**).

Table 3. Associations of FIX levels with spontaneous bleeding events after fitting an age-adjusted shared frailty model: rFIXFc versus N9-GP

Outcome: recurrent bleeding	rFIXFc						N9-GP						*p*-value for interaction between FIX levels and product type
	No. of bleeds	No. of patients with a bleed	Total no. of patients	Person-days	HR (95% CI)	*p*-value	No. of bleeds	No. of patients with a bleed	Total no. of patients	Person-days	HR (95% CI)	*p*-value	
FIX (IU/dL) categories													0.008
First quartile (FIX level ≤8.6)	22	7	11	4,521	1		2	2	6	3,456	1		
Second quartile (8.6< FIX level ≤20.1)	35	10	12	7,396	0.68 (0.32–1.42)	0.31	10	7	9	3,913	11.73 (0.80–171.38)	0.072	0.045
Third quartile (20.1 <FIX level ≤34.7)	12	7	8	2,873	0.56 (0.21–1.47)	0.24	26	11	13	7,583	9.43 (0.70–127.63)	0.091	0.048
Fourth quartile (FIX level >34.7)	8	3	4	620	3.34 (0.99–11.30)	0.052	52	15	16	13,504	7.33 (0.55–97.35)	0.131	0.59

CI, confidence interval; FIX, factor IX; HR, hazard ratio; N9-GP, nonacog beta pegol; rFIXFc, recombinant FIX fusion protein.

Discriminatory threshold analysis

- For rFIXFc, the trough level of all non-bleeders was ≤25 IU/dL, and approximately 50% of bleeders bled at FIX levels ≤20 IU/dL (**Table 4**).
- For N9-GP, the trough levels for all non-bleeders was ≤15 IU/dL, whereas 50% of bleeders bled at FIX levels ≤60 IU/dL (**Table 4**).

Table 4. Discriminatory ability of predicted FIX level (highest for bleeders and lowest trough for non-bleeders) in predicting spontaneous bleeds (yes or no) among patients who received rFIXFc versus N9-GP

FIX level (IU/dL)	rFIXFc*		N9-GP**	
	Se among bleeders	Sp among non-bleeders	Se among bleeders	Sp among non-bleeders
No. of patients	14	9	18	9
Decile cut points				
≤3.64	0/14 (0.00)	6/9 (66.67)	0/18 (0.00)	6/9 (66.67)
≤6.87				
≤9.94	1/14 (7.14)	6/9 (66.67)	0/18 (0.00)	8/9 (88.89)
≤15.16	4/14 (28.57)	8/9 (88.89)	0/18 (0.00)	9/9 (100.00)
≤20.11	6/14 (42.86)	8/9 (88.89)	1/18 (5.56)	9/9 (100.00)
≤25.27	9/14 (64.29)	9/9 (100.00)	2/18 (11.11)	9/9 (100.00)
≤30.84	10/14 (71.43)	9/9 (100.00)	3/18 (16.67)	9/9 (100.00)
≤40.95	12/14 (85.71)	9/9 (100.00)	6/18 (33.33)	9/9 (100.00)
≤58.42	13/14 (92.86)	9/9 (100.00)	9/18 (50.00)	9/9 (100.00)
Additional cut points				
≤70	-	-	9/18 (50.00)	9/9 (100.00)
≤80	-	-	12/18 (66.67)	9/9 (100.00)
≤95	-	-	15/18 (83.33)	9/9 (100.00)
≤100	-	-	16/18 (88.89)	9/9 (100.00)

N9-GP, nonacog beta pegol; rFIXFc, recombinant FIX fusion protein; Se, sensitivity; Sp, 1-Specificity. *There was no predicted factor level between 6.87 and 9.94 IU/dL. **There was no predicted factor level between 6.87 and 9.94 IU/dL.

- A similar discriminatory pattern was observed for patients with only severe hemophilia B. Non-bleeders treated with rFIXFc or N9-GP exhibited trough levels of ≤25 IU/dL and ≤15 IU/dL, respectively. Approximately 50% of the bleeders experienced bleeds at FIX level of ≤20 IU/dL for rFIXFc and ≤60 IU/dL for N9-GP.
- **Table 5** presents the median predicted FIX levels for the 1st to subsequent spontaneous bleeds for patients who received rFIXFc or N9-GP, stratified by the severity of hemophilia B.
  - For rFIXFc, FIX levels at repeated bleeding events remained low and comparable across both severe and moderate cases.
  - N9-GP patients had considerably higher predicted FIX levels during the bleeding events, with median levels often in the normal to near-normal range for both severities.

Table 5. Predicted FIX level (IU/dL) at the 1st spontaneous bleed and up to the 9th spontaneous bleed among patients with hemophilia B

	rFIXFc			N9-GP		
	Overall	Severe	Moderate	Overall	Severe	Moderate
Total no. of bleeds	77	40	37	90	60	30
Median predicted FIX level (IU/dL) at						
1st bleed	13 (4, 20), 14	13 (4, 20), 10	8 (1, 21), 4	33 (18, 43), 18	28 (17, 37), 13	40 (40, 43), 5
2nd bleed	17 (9, 24), 13	16 (6, 24), 9	19 (13, 39), 4	38 (23, 66), 16	27 (19, 56), 11	44 (44, 75), 5
3rd bleed	11 (8, 16), 9	10 (8, 16), 6	11 (4, 34), 3	35 (23, 66), 12	32 (22, 81), 8	38 (29, 46), 4
4th bleed	9 (3, 18), 8	9 (5, 17), 5	9 (1, 33), 3	49 (41, 75), 10	65 (39, 78), 7	48 (47, 49), 3
5th bleed	23 (9, 30), 7	16 (10, 26), 4	26 (1, 67), 3	42 (26, 58), 6	53 (37, 59), 4	26 (15, 37), 2
6th bleed	7 (6, 10), 5	7 (6, 7), 2	10 (1, 54), 3	56 (35, 59), 5	59 (35, 71), 3	36 (16, 56), 2
7th bleed	10 (7, 13), 5	10 (7, 13), 2	10 (1, 39), 3	50 (39, 51), 5	39 (25, 51), 3	54 (50, 58), 2
8th bleed	11 (10, 14), 4	14 (11, 17), 2	10 (8, 11), 2	33 (31, 58), 4	32 (29, 34), 2	57 (32, 83), 2
9th bleed	9 (4, 13), 2	-	9 (4, 13), 2	47 (33, 65), 4	33 (30, 36), 2	65 (58, 72), 2

FIX, factor IX; N9-GP, nonacog beta pegol; rFIXFc, recombinant FIX fusion protein.
Data are presented as median (25th, 75th percentiles); n, number of patients.

Strengths and limitations

- A key strength of this study was the availability of plasma FIX activity data, enabling more precise evaluation.
- The study relies on existing medical records, which may not represent the entire population of PWHB.
- The findings may not be generalizable to all PWHB, particularly those outside Canada or on different treatment regimens.

Conclusion

- **In hemophilia B, high plasma levels for different products do not necessarily indicate improved bleed protection, similarly, low plasma FIX levels may not necessarily indicate reduced protection.**
- **For patients experiencing breakthrough bleeds at high plasma FIX levels, switching to an alternative concentrate with a different PK profile may be more effective than increased dosing.**

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