Personalization of hemophilia treatment by pharmacokinetic-guided dosing

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CHAPTER 12

In silico comparison of three extended half-life factor IX products reveals major differences in factor IX pharmacokinetics

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Abstract

Extended half-life (EHL) factor IX (FIX) products require less frequent infusions to maintain trough target activities in hemophilia B patients when compared to standard half-life (SHL) products. Consequently, more time with relative low FIX activities is observed, which may reduce hemostatic efficacy. In this study, the pharmacokinetic (PK) characteristics of three EHL-FIX products were evaluated and compared to SHL recombinant FIX (rFIX). Activity-time profiles of PEGylated FIX (N9-GP), FIX linked with human albumin (rIX-FP), FIX coupled to human IgG1 Fc-domain (rFIXFc), and SHL-rFIX were simulated for 10,000 patients during steady-state dosing of 40 $IUkg^{-1}$ once weekly (EHL-FIX products) and biweekly (rFIX) using the published product specific population PK models. Half-lives of the EHL-products were 98, 104 and 83 hours for N9-GP, rIX-FP, and rFIXFc, respectively, versus 22 hours for rFIX. Between the EHL-products, exposure was different with area under the curve (AUC) values of 58.4, 49.6, and 12.1 $IUhmL^{-1}$ and time above 10% values of 168, 168 and 36 hours for N9-GP, rIX-FP, and rFIXFc, respectively. When comparing EHL-products, not only half-life but also exposure, as exemplified by the AUC, must be considered. This study has major implications for dosing regimens of EHL-FIX products in real–life.

Key points

- Despite comparable half-lives, EHL-FIX products exhibit different exposures and time intervals above and below a specific target activity.

- EHL-FIX products should not only be judged on their augmented half-life but also on exposure and, therefore, potential hemostatic efficacy.

Introduction

Hemophilia B patients exhibit a deficiency of coagulation factor IX (FIX) resulting in bleeding, specifically in joints and muscles.[1] It has been demonstrated that in patients with moderate hemophilia, defined as a baseline FIX activity of ≥1% (0.01 $IUmL^{-1}$), spontaneous bleeding occurs infrequently and development of arthropathy is delayed.[2,3] Therefore, severe and some moderate hemophilia B patients administer FIX concentrate prophylactically to maintain trough activities >1%.[4] Trough activities >1% may, however, still be insufficient to protect patients from spontaneous bleeding.[5] In hemophilia A patients, Collins et al. demonstrated that longer time intervals spent with factor VIII activities >1% resulted in lower annualized bleeding rates.[6] This may also be the case for hemophilia B patients. Therefore, higher FIX trough activities may be required for some patients, depending on bleeding tendency, level of physical activity and joint status.[7] As a result, not only peak FIX activity, but also area under the activity versus time curve (AUC) and time spent with FIX activities above 3%, 5% and 10% are expected to be important determinants to predict the risk of bleeding episodes.

Efforts have been made to modify the pharmacological properties of FIX products in order to extend its terminal half-life and/or augment it's *in vivo* hemostatic function.[8–10] Currently, three extended half-life (EHL) FIX products are widely available: PEGylated FIX (N9-GP), FIX linked with recombinant human albumin (rIX-FP), and FIX coupled to the human IgG1 Fc domain (rFIXFc).[11,12]Santagostino et al, in their phase 3 study, demonstrate efficacy and safety of recombinant fusion protein linking coagulation factor IX (FIX Whereas standard half-life (SHL) FIX products are administered twice weekly to maintain target FIX trough activities, EHL-FIX products can be administered once weekly or less.[13] One of the greatest advantage of these EHL-FIX products is the reduction in frequency of infusion, which is more convenient for the patient in most circumstances. On the contrary, less frequent administration of EHL-FIX products may result in longer time intervals at relatively low FIX activities, thereby diminishing the hemostatic efficacy of prophylaxis.

In this study, the pharmacokinetic (PK) characteristics of three currently available EHL-FIX products were compared to those of a widely used SHL-rFIX concentrate.

Methods

Monte Carlo simulations were performed to produce FIX activity versus time profiles of three EHL-FIX products (N9-GP (Refixia®, Novo Nordisk A/S, Denmark), rIX-FP (Idelvion®, CSL Behring GmbH, Germany), and rFIXFc (Alprolix®, Swedish Orphan Biovitrum AB, Sweden)) and one SHL-rFIX product (BeneFIX®, Pfizer, United Kingdom) in 10,000 virtual patients. [14] The simulations were performed in NONMEM v7.4.1. using population PK parameters reported in literature.[15–18] R software (v3.4.3) was used to create the population of 10,000 virtual severe hemophilia B patients.[19] Simulated age and bodyweight ranged from 10 to 65 years and from 56 to 90 kg, respectively, reflecting the population on which the PK models were originally built.

In the simulations, steady-state PK was present in all patients, receiving 40 $IUkg^{-1}$ of EHL-FIX once weekly and 40 $IUkg^{-1}$ SHL-rFIX twice-weekly. For each virtual patient, the following PK parameters were calculated: terminal elimination half-life, AUC (from 0 to 168 hours), maximum activity, FIX trough activity. Moreover, the time below and above 1%, 3%, 5%, and 10% were calculated. Furthermore, individual PK parameters were used to calculate the dose of FIX concentrate needed to achieve a steady-state FIX trough activity of 1%, 3%, 5%, and 10%.

Results and Discussion

The distributions of age and body weight of the 10,000 virtual patients with severe hemophilia B are depicted in Figure 1A. Figure 1B shows the FIX activity versus time profile of the median FIX activities observed during steady-state dosing of 40 $IUkg^{-1}$ for the studied FIX products. Clearly, FIX activities peak following the intravenous administration and, subsequently, rapidly decrease due to distribution with a slower decrease during the elimination phase. However, Figure 1B and 1C show that the exposure of N9-GP and rIX-FP were different from that of rFIXFc and rFIX.

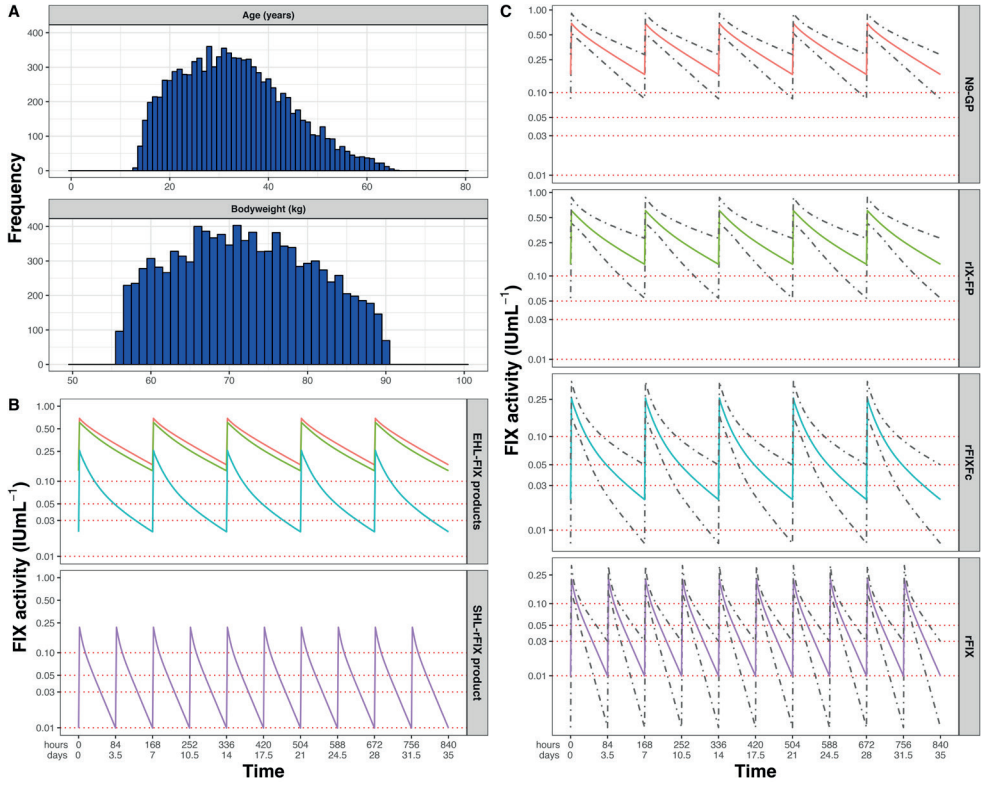

Figure 1. Simulated patient characteristics and FIX activities. IU: international units. SHL: short half-life. EHL: extended half-life. A. Distribution of age and body weight for the simulated population of 10,000 severe hemophilia B patients. B. Median FIX activities versus time from N9-GP (orange), rIX-FP (green), rFIXFc (blue), and rFIX (purple) for 10,000 patients during steady-state dosing of 40 IUkg^{-1} once weekly (EHL-products) and 40 IUkg^{-1} twice weekly (rFIX). The dashed red lines depict the target trough activities. C. Median simulated FIX activities from N9-GP (orange), rIX-FP (green), rFIXFc (blue), and rFIX (purple) versus time with the 2.5th and 97.5th percentiles (grey dashed lines) of the FIX activities. Note the logarithmically transformed y-axis.

Elimination half-lives of the EHL-FIX products were comparable with values of 98, 104, and 83 hours for N9-GP, rIX-FP, and rFIXFc, respectively. As expected, these parameters were 4 to 5-fold longer than for the SHL-rFIX product with a value of 22 hours (Table 1). Interestingly, the increased half-life of the various EHL-FIX products did not result in comparable increases in exposure (AUC). Median AUCs of N9-GP (58.4 IUhmL^{-1}) and rIX-FP (49.6 IUhmL^{-1}) were 5 and 4 times higher, respectively, than the AUC of rFIXFc (12.1 IUhmL^{-1}). In general, after administration of 40 IUkg^{-1}, higher peak activities were observed for N9-GP and rIX-FP in comparison with rFIXFc. This is also reflected in both the calculated trough activity which is 0.17, 0.14, and 0.02 IUmL^{-1} for N9-GP, rIX-FP, and rFIXFc, respectively, and in the time above and below 3%, 5%, and 10% (Table 1).

Table 1. Simulated PK parameters for steady-state dosing of 40 IUkg^{-1}

	N9-GP		rIX-FP		rFIXFc		rFIX	
Parameter	**Median**	**Range 90%**	**Median**	**Range 90%**	**Median**	**Range 90%**	**Median**	**Range 90%**
Terminal elimination half-life (h)	98.2	[70.1 - 146.0]	103.9	[73.4 - 158.2]	82.6	[47.4 - 158.5]	21.5	[13.9 - 34.0]
AUC (IU h mL^{-1})	58.4	[44.3 - 77.2]	49.6	[34.6 - 71.1]	12.1	[8.0 - 18.1]	10.1	[7.31 - 13.9]
Maximum activity (IU mL^{-1})	0.71	[0.56 - 0.91]	0.62	[0.46 - 0.85]	0.42	[0.27 - 0.66]	0.42	[0.22 - 0.79]
Trough activity (IU mL^{-1})	0.17	[0.10 - 0.26]	0.14	[0.06 - 0.26]	0.021	[0.009 - 0.044]	0.010	[0.002 - 0.026]
Time above 1% (h)	168.0	[168.0 - 168.0]	168.0	[168.0 - 168.0]	168.0	[156.5 - 168.0]	166.5	[111.0 - 168.0]
Time above 3% (h)	168.0	[168.0 - 168.0]	168.0	[168.0 - 168.0]	129.5	[73.9 - 168.0]	98.6	[64.9 - 154.6]
Time above 5% (h)	168.0	[168.0 - 168.0]	168.0	[168.0 - 168.0]	81.0	[48.0 - 150.0]	67.9	[44.5 - 106.8]
Time above 10% (h)	168.0	[152.5 - 168.0]	168.0	[118.0 - 168.0]	35.9	[20.8 - 64.4]	30.3	[19.8 - 48.2]
Time below 1% (h)	0	[0 - 0]	0	[0 - 0]	0	[0 - 11.5]	1.5	[0 - 57.0]
Time below 3% (h)	0	[0 - 0]	0	[0 - 0]	38.5	[0 - 94.1]	69.4	[13.4 - 103.1]
Time below 5% (h)	0	[0 - 0]	0	[0 - 0]	87.0	[18.0 - 120.0]	100.1	[61.2 - 123.5]
Time below 10% (h)	0	[0 - 15.5]	0	[0 - 49.9]	132.1	[103.6 - 147.2]	137.7	[119.8 - 148.2]
Dose to achieve target activity								
Target trough 1% (IU kg^{-1})	2.41	[1.52 - 4.19]	2.89	[1.57 - 6.23]	18.9	[9.0 - 46.0]	82*	[31 - 322]
Target trough 3% (IU kg^{-1})	7.23	[4.55 - 12.6]	8.67	[4.72 - 18.7]	56.8	[26.9 - 137.9]	245*	[92 - 966]
Target trough 5% (IU kg^{-1})	12.1	[7.6 - 20.9]	14.4	[7.9 - 31.1]	94.6	[44.9 - 229.8]	409*	[153 - 1610]
Target trough 10% (IU kg^{-1})	24.1	[15.2 - 41.9]	28.9	[15.7 - 62.3]	189.2	[89.8 - 459.6]	817*	[306 - 3220]

IU: international units; AUC: area under the curve. The steady-state levels of the EHL-FIX products were achieved by dosing 40 IUkg^{-1} every 168 hours, whereas steady-state FIX activities for rFIX were achieved by dosing 40 IUkg^{-1} every 84 hours. * As rFIX doses were administrated twice weekly, the calculated value depicts the sum of the two doses administered per week.

Although a weekly dose of 40 IUkg^{-1} produces median FIX activities above 1% during the complete dosing period of 168 hours (one week) for each of the EHL-FIX products, significant differences were observed for a target trough activities of 10%. In the latter case, median values for the time above a target activity of 10% were 168, 168 and 36 hours for N9-GP, rIX-FP, and rFIXFc, respectively. The median time below 10% for N9-GP and rIX-FP was zero, whereas the median time below 10% of rFIXFc and rFIX was comparable with respective values of 132 and 138 hours. Interestingly, once weekly dosing of 40 IUkg^{-1} rFIXFc produced similar values for AUC and time above 10% as compared with dosing of rFIX twice weekly.

In Table 1, the weekly doses to maintain specific target trough activities are presented. The required dose of rIX-FP was slightly higher than for N9-GP, whereas the dose of rFIXFc was a 7-fold higher; respective doses for a target trough activity of 1% were 2.4, 2.9, and 19 IUkg^{-1} once weekly for N9-GP, rIX-FP, and rFIXFc, respectively. In comparison with rFIX, the weekly dose for a target trough activity of 1% was 33, 29, and 4.3-fold lower for N9-GP, rIX-FP, and rFIXFc, respectively. The differences between the EHL-FIX products and SHL-rFIX and among the EHL-FIX products were independent of the target activity.

In this study, the simulated trough activities of the EHL-FIX products at 168 hours were in agreement with those clinically observed and reported in literature.[15–17] However, recently, trough activities have been reported for N9-GP, which were higher than those simulated.[20,21] The cause of this difference is unclear. So far, no updated population PK parameters, which are required to perform Monte Carlo simulations, have been reported for N9-GP.

Currently available EHL-FIX products definitely decrease the burden of care by reducing the frequency of prophylactic intravenous infusions in severe hemophilia B patients.[22] The simulations in this study show that these EHL-FIX products should not only be judged on the basis of their (augmented) half-life but also on their exposure and, therefore, their potential hemostatic efficacy. Despite their comparable half-lives, the investigated EHL-FIX products exhibit different AUCs and different time intervals above and below a specific target activity. Longer periods of time at relatively higher FIX activities may be beneficial in individual patients on prophylaxis considering bleeding phenotype, physical activity, and joint status. This study has major implications for dosing regimens of EHL-FIX products in real–life and highlights the importance of PK assessments when implementing novel clotting factor products.

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