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ORIGINAL ARTICLE

Assessing bleeding rates, related clinical impact and factor utilization in German hemophilia B patients treated with extended half-life rIX-FP compared to prior drug therapy

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ABSTRACT

Objective: An extended half-life factor IX (FIX) fusion protein linking recombinant FIX with recombinant human albumin (rIX-FP), indicated for the treatment of hemophilia B, was approved by the European Medicines Agency in May 2016. We aimed to compare clinical outcomes and drug utilization in patients who switched from prior FIX therapies to rIX-FP.

Methods: Anonymized patient chart data were collected from German institutions treating patients with hemophilia B. Patients were included if they had been treated with rIX-FP for ≥8 weeks at the time of data collection. Bleeding rates and FIX consumption were compared between rIX-FP and patients' prior FIX products.

Results: Data were obtained for 81 male patients treated with rIX-FP, including 59 who received prophylaxis with both their prior drug and rIX-FP (prophylaxis-to-prophylaxis group). Mean factor consumption in this group was 44.2 IU/kg/wk for rIX-FP compared with 82.3 IU/kg/wk for all prior FIX products. In addition, intra-patient analysis of factor consumption showed lower consumption of rIX-FP compared with prior FIX in 56 of 59 patients. Among the patients for whom bleed data were available ($n = 42$), annualized bleeding rate decreased from a mean (standard deviation) of 2.6 ± 2.9 on prior product to 0.3 ± 0.6 on rIX-FP. The proportion of patients with zero bleeds increased from 24% with prior therapy to 81% with rIX-FP.

Conclusion: rIX-FP was associated with substantial reductions in bleeding rates and consumption of FIX compared with standard half-life products that require more frequent administration.

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Drug utilization; factor IX; hemophilia B; rIX-FP fusion protein; treatment outcome

Introduction

Continuous prophylactic coagulation factor replacement therapy from a young age has been found to provide better outcomes than on-demand treatment[1] and is now the gold standard of care for patients with severe hemophilia[2]. Prophylaxis in children can prevent joint damage[3], and adults report better joint health and health-related quality of life with prophylaxis than with on-demand treatment[4,5]. Prior to 2016, plasma-derived (pd) and standard recombinant factor IX (FIX) products were the only available therapeutic options for FIX replacement treatment in Germany. These drugs are typically infused intravenously twice a week, a treatment burden that can contribute to delayed adoption of prophylaxis, or nonadherence to the prescribed regimen[6]. In a recent survey among hemophilia patients and parents of children with hemophilia, conducted in Germany, Austria and Switzerland, one of the most frequently reported unmet needs was to lower the treatment burden by reducing the frequency of factor injections.[7] The recent introduction of extended half-life (EHL) recombinant FIX (rFIX) products, which can be infused once every one to two weeks, may present an opportunity to achieve better protection against bleeds across a larger patient population through higher prophylaxis rates and increased adherence.

In Germany, the most commonly prescribed standard half-life (SHL) FIX products include the recombinant nonacog alfa (BeneFIX, Pfizer) as well as a few plasma-derived products. In May 2016, the European Medicines Agency (EMA) approved two EHL FIX products: rIX-FP (albutrepenonacog alfa, IDELVION, CSL Behring) and rFIXFc (eftrenonacog alfa, Alprolix, Sobi). rIX-FP, a recombinant fusion protein linking rFIX with recombinant human albumin, is produced as a single protein with a cleavable linker between rFIX and albumin. Albumin has a long half-life in part because it is protected from degradation by binding to the neonatal Fc receptor (FcRn). Albumin fusion technology increases the half-life of rIX-FP compared with rFIX.[8] rFIXFc is a fusion protein in which the Fc fragment of immunoglobulin G is fused

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to rFIX. Fc fusion prolongs the half-life of FIX as it binds to FcRn, which allows endosomal recycling of FIX.[9] These EHL FIX products offer significant improvements in half-life compared to standard replacement factors, with mean terminal half-lives of 102 hours for rIX-FP and 82 hours for rFIXFc compared with 15–24 hours for rFIX.[10,11] A third EHL FIX, N9-GP (nonacog beta pegol, Refixia, Novo Nordisk) was approved by the EMA in June 2017. N9-GP is a conjugation between FIX and polyethylene glycol (PEG),[12] where pegylation aims at protecting FIX from proteolytic enzymes. This product was not available in Germany at the time of this study.

In the present study, we set out to understand how one of these EHL products, rIX-FP, was used in a real-world setting, and how clinical outcomes and utilization compared to prior treatment with SHL products.

Methods

A retrospective review of pre-existing medical records collected from Comprehensive Care Centers (CCCs), Hemophilia Treatment Centers (Hämophilie-Behandlungs-Einrichtung [HBE]) or smaller regional Hemophilia Treatment Centers (Hämophilie-Behandlung [HB]) across Germany was conducted for hemophilia B patients currently receiving rIX-FP. To qualify for inclusion in the analysis, patients must have received at least 8 weeks of treatment with rIX-FP. If a prior FIX product was used, a minimum of 8 weeks of treatment on the prior product was required to be included in the analysis. De-identified data were provided by treating physicians during January and February, 2018. The study obtained only pre-existing data from patients who were never identified to researchers and therefore did not require informed consent. The study was submitted to an institutional review board and was determined to be exempt under category 4 'Secondary research for which consent is not required'.

Data were collected for age, sex, weight, severity of hemophilia B, start date of rIX-FP, regimen (prophylaxis vs. on demand), dosing (dose and frequency) of rIX-FP and prior FIX product, and a number of bleeds reported to the treating physician within the preceding 2 to 12 months of treatment. Prophylaxis was defined as prescribed prophylactic treatment to prevent bleeding through regular infusions over the time period analyzed in this study. All patients receiving infusions to treat a bleed or for perioperative management were defined as on-demand. Consistent with product labeling, adult and adolescent patients (collectively referred to as the adult group in the rest of this manuscript) were defined as those 12 years and older; pediatric patients were 11 years or younger. The target sample size was approximately 85 patients, representing approximately 50% of the estimated patient population treated with rIX-FP at the time of data collection.

Primary outcome measures were bleeding rate and consumption of replacement factor in patients receiving prophylaxis with rIX-FP compared to the prior product, both intra-patient and for the entire patient group. Calculation of replacement factor utilization was based on the most recent prescription of each product, and reported as international units of product per kilogram of body weight per week (IU/kg/wk), defined as dose per infusion (IU) multiplied by the number of infusions per week and divided by the patient's weight (kg). The annualized bleeding rate (ABR) was calculated as the number of reported bleeding events divided by the number of months in the reporting time window (8 weeks to 12 months) and multiplied by 12.

Results

Twenty-four sites (including CCCs, HBE, and HB) provided data for a total of 81 patients treated with rIX-FP for at least 8 weeks. The mean duration of therapy with rIX-FP was 39 weeks (median, 37; range 8–89). The majority of patients (90%) had received rIX-FP for at least 12 weeks or more and 68% of patients had at least 26 weeks of treatment with rIX-FP. For all patients who had been treated with another FIX product ($n = 74$), the 52 weeks preceding the switch to rIX-FP were analyzed. All patients were male, 67 were adults and 14 were children; baseline characteristics, along with prior replacement product and treatment regimen, are displayed in Table 1. Of these 81 patients, 72 (89%) were treated prophylactically with rIX-FP, including 59 (73%) who were also on prophylaxis with their prior drug (prophylaxis-to-prophylaxis group).

Bleeding rates

Data for bleeding events were available for 51 patients and are presented in Table 2. In these 51 patients, the mean duration of treatment on rIX-FP was 36.9 weeks (median, 33; range 8–89); 4 (7.8%) patients had been treated with rIX-FP for 8–12 weeks, 14 (27.5%) for 13–25 weeks, and 33 (64.7%) for at least 6 months (26 weeks or more).

In patients on prophylaxis both prior to, and after switching to rIX-FP (prophylaxis-to-prophylaxis, $n = 42$), mean duration of treatment on rIX-FP was 37.2 weeks (range 8–89) and the mean duration of treatment analyzed on prior drug was at least 52 weeks. Of the 42 patients in the prophylaxis-to-prophylaxis group, 76% had severe disease, 19% had moderate disease and 5% had mild disease. In these patients, mean ± standard deviation ABR with rIX-FP was 0.3 ± 0.6 compared with 2.6 ± 2.9 on the prior FIX product. Of these patients, 81% had zero bleeds while on rIX-FP, resulting in a median ABR of 0 with rIX-FP, compared to 24% with the prior FIX product (median ABR, 1.2). In the subgroup of patients who switched from nonacog alfa to rIX-FP ($n = 28$), mean ABR decreased from 3.2 ± 3.1 to 0.4 ± 0.7, and the number of patients with zero bleeds increased from 14% to 75%. In those who switched from pdFIX ($n = 14$), mean ABR decreased from 1.4 ± 1.9 to 0.4 ± 0.5 with rIX-FP, and the number of patients with zero bleeds increased from 43 to 93%.

When alternative criteria of at least 12 weeks and at least 26 weeks of treatment with rIX-FP were used in the analysis of ABR in the prophylaxis-to-prophylaxis group, similar results were found to those previously stated. For example, when only patients with at least 12 weeks of treatment with rIX-FP

Table 1. Patient characteristics.

	All patients ($n = 81$)	Severe ($n = 54$)	Moderate/Mild ($n = 27$)	Adult (≥12 years) ($n = 67$)	Pediatric (0–11 years) ($n = 14$)
Age (years)					
Mean ± SD	25.0 ± 17.0	23.2 ± 15.5	30.0 ± 20.3	31.4 ± 14.4	4.6 ± 2.3
Median (range)	24.0 (2.0–76.0)	23.5 (2.0–64.0)	28.0 (2.5–76.0)	26.0 (12.0–76.0)	4.0 (2.0–10.0)
Weight (kg)					
Mean ± SD	68.4 ± 24.1	67.8 ± 23.2	69.9 ± 23.2	76.8 ± 12.2	22.6 ± 12.7
Median (range)	73.0 (12.0–125.0)	70.5 (13.0–125.0)	77.0 (12.0–100.0)	75.0 (43.0–125.0)	16.5 (12.0–48.7)
Severity					
Severe, *n* (%)	54 (66.7)	n/a	n/a	45 (67.2)	9 (64.3)
Moderate/Mild, *n* (%)	27 (33.3)			22 (32.8)	5 (35.7)
Current regimen					
Prophylaxis, *n* (%)	72 (88.9)	54 (100)	18 (66.7)	60 (89.6)	12 (85.7)
On-demand, *n* (%)	9 (11.1)	0 (0)	9 (33.3)	7 (10.4)	2 (14.3)
Prior regimen					
Prophylaxis, *n* (%)	59 (72.8)	44 (81.5)	15 (55.6)	53 (79.1)	6 (42.9)
On-demand, *n* (%)	16 (19.8)	6 (11.1)	10 (37.0)	12 (17.9)	4 (28.6)
Untreated, *n* (%)	6 (7.4)	4 (7.4)	2 (7.4)	2 (3.0)	4 (28.6)
Prior drug used					
Nonacog alfa, *n* (%)	51 (63.0)	37 (68.5)	14 (51.9)	42 (62.7)	9 (64.3)
pdFIX, *n* (%)	24 (29.6)	13 (24.1)	11 (40.7)	23 (34.3)	1 (7.1)

Abbreviation. pd, Plasma-derived.

Table 2. Bleeding rates with rIX-FP compared to prior product for patients with reported bleed information and at least 8 weeks of treatment with rIX-FP.

	rIX-FP		All prior FIX	Nonacog alfa	pdFIX (all)
	All	Q7d			
Prophylaxis-to-prophylaxis patients					
ABR (mean ± SD)	0.3 ± 0.6 ($n = 42$)	0.4 ± 0.7 ($n = 28$)	2.6 ± 2.9 ($n = 42$)	3.2 ± 3.1 ($n = 28$)	1.4 ± 1.9 ($n = 14$)
# with 0 bleeds (%)	34 (81)	21 (75)	10 (24)	4 (14)	6 (43)
On-demand-to-prophylaxis patients					
ABR (mean ± SD)	0.2 ± 0.4 ($n = 5$)	0.3 ± 0.5 ($n = 4$)	5.3 ± 2.8 ($n = 5$)	4.4 ± 3.4 ($n = 3$)	6.5 ± 2.1 ($n = 2$)
# with 0 bleeds (%)	4 (80)	3 (75)	0 (0)	0 (0)	0 (0)

Abbreviations. ABR, Annualized bleeding rate; pdFIX, Plasma-derived factor IX; Q7d, Every 7 days.

Table 3. Bleeding rates with rIX-FP prophylaxis compared to prophylaxis on prior product for patients aged ≥12 years and 0–11 years with reported bleed information and at least 8 weeks of treatment with rIX-FP.

	rIX-FP		All prior FIX	Nonacog alfa	pdFIX (all)
	All	Q7d			
≥12 years of age					
ABR (mean ± SD)	0.2 ± 0.6 ($n = 38$)	0.3 ± 0.7 ($n = 25$)	2.8 ± 3.0 ($n = 38$)	3.5 ± 3.2 ($n = 25$)	1.5 ± 2.0 ($n = 13$)
# with 0 bleeds (%)	32 (84)	20 (80)	9 (24)	4 (16)	5 (38)
0–11 years of age					
ABR (mean ± SD)	0.8 ± 1.0 ($n = 4$)	0.2 ± 0.6 ($n = 3$)	0.8 ± 0.6 ($n = 4$)	1.1 ± 0.2 ($n = 3$)	0.0 ± 0.0 ($n = 1$)
# with 0 bleeds (%)	2 (50)	1 (33)	1 (25)	0 (0)	1 (100)

Abbreviations. ABR, Annualized bleeding rate; pdFIX, Plasma-derived factor IX.

were included, mean ABR with rIX-FP ($n = 38$), nonacog alfa ($n = 27$) and pdFIX ($n = 11$) were 0.3 ± 0.6, 3.3 ± 3.1 and 1.5 ± 2.1, respectively. Of these patients, 79% had zero bleeds while on rIX-FP compared to 15% and 46% with the prior nonacog alfa and pdFIX, respectively. When only patients with at least 26 weeks treatment on rIX-FP were included, the corresponding mean ABRs were 0.3 ± 0.7, 2.8 ± 2.7 and 2.6 ± 2.8 ($n = 26$, 21, and 5). Of these patients, 81% had zero bleeds while on rIX-FP compared to 19% and 40% with prior nonacog alfa and pdFIX, respectively.

In patients aged ≥12 years who were on prophylaxis, both prior to and after switching to rIX-FP (prophylaxis-to-prophylaxis, $n = 38$), mean ABRs similar to those observed in the overall prophylaxis-to-prophylaxis patient group were reported (Table 3). Mean ABRs were lower with rIX-FP prophylaxis compared with prophylaxis on prior FIX, and the number of patients with zero bleeds also increased after the switch. Results in those patients 0–11 years of age were less meaningful as there was only data for four patients, as presented in Table 3.

Among the five patients who switched from on-demand treatment to prophylaxis with rIX-FP, the mean duration of treatment on rIX-FP was 45 weeks (median, 50; range 32–54), and the duration of treatment analyzed on the prior drug was 52 weeks. Mean ABR decreased from 5.3 ± 2.8 to 0.2 ± 0.4 (Table 2). Four (80%) of these patients experienced a reduction in ABR (range 1–8) to zero, and one patient showed a reduction in ABR from 5 to 1. These results also should be interpreted with caution due to the small sample size.

Dosing regimen

Of the 72 patients on prophylaxis with rIX-FP, 68% infused factor once a week, and 22% infused every 9 or more days. In contrast, 66% of the 59 patients previously on prophylaxis

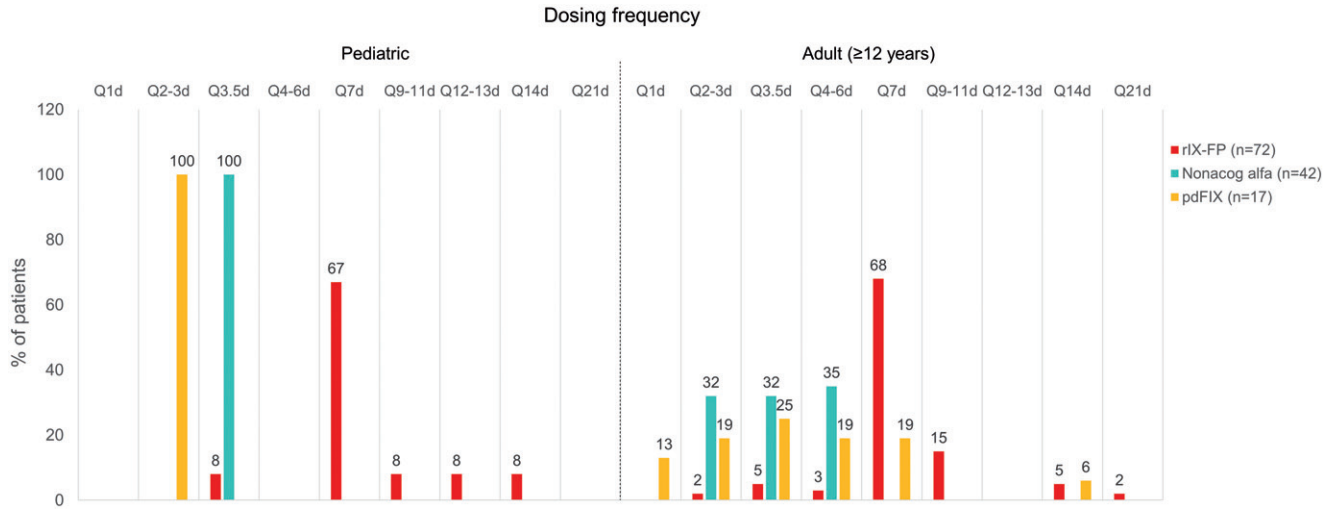

Figure 1. Frequency of prophylaxis by type of replacement product. Distribution of dosing frequencies within pediatric (left) and adult (right) patients on current (rIX-FP [red]) and prior product (nonacog alfa [blue], or pdFIX [yellow]). The dosing frequency is labelled as Qnd when patients infuse every *n* day(s). A twice a week infusion schedule was labelled as Q3.5d. pdFIX, Plasma-derived factor IX.

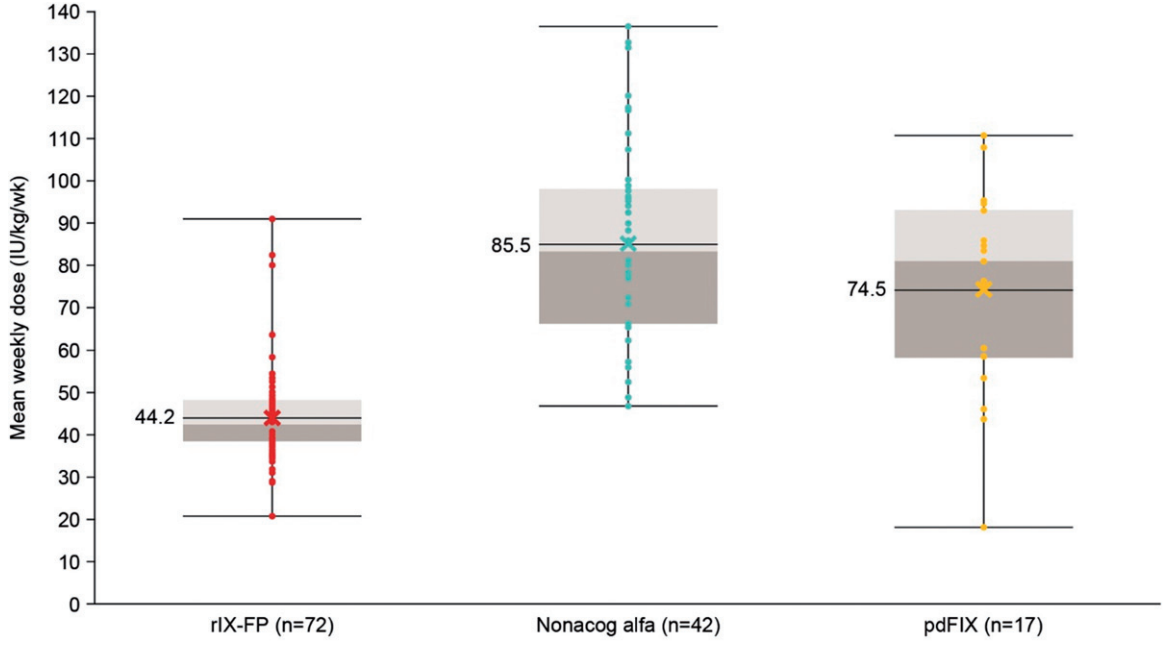

Figure 2. Doses by type of replacement product for all patients receiving prophylaxis. Individual mean patient doses in IU/kg/wk are plotted on the y-axis for each product or product category. X-mark and label indicate mean, whiskers indicate minimum and maximum values, dark grey zone indicates 2nd quartile range (25th–50th percentile), light grey zone indicates 3rd quartile (50th–75th percentile), boundary between grey zones indicates median. pdFIX, Plasma-derived factor IX.

with SHL products infused at least twice a week, and 7% infused once a week or at a lower frequency. Similar profiles were seen in both adult and pediatric patients, with dosing intervals of 7 days or longer in 88% and 91% of patients, respectively, during treatment with rIX-FP compared with in 0% of both adult and pediatric patients during treatment with nonacog alfa (Figure 1).

Factor consumption

The mean weekly dose by type of product (rIX-FP, nonacog alfa, or pdFIX) for all patients on prophylaxis is shown in Figure 2. Mean weekly dose of rIX-FP was 44.2 IU/kg/wk ($n = 72$; range 21–91). Mean weekly dose on nonacog alfa was almost two-times higher, at 85.5 IU/kg/wk ($n = 42$; range 47–136), and mean weekly dose of all pdFIX products was 74.5 IU/kg/wk ($n = 17$; range 18–111). When corresponding analyses were performed for all patients aged ≥12 years mean weekly dose of rIX-FP was 44.1 IU/kg/wk ($n = 60$; range 21–82); mean weekly dose of nonacog alfa was 84.3 IU/kg/wk ($n = 37$; range 47–133); and mean weekly dose of all pdFIX products was 74.0 IU/kg/wk ($n = 16$; range 18–111). In turn, the corresponding results for all patients aged 0–11 years were: mean weekly dose of rIX-FP was 45.0 IU/kg/wk ($n = 12$; range 29–91); mean weekly dose of nonacog alfa was 94.2 IU/kg/wk ($n = 5$; range 57–136); and mean weekly dose

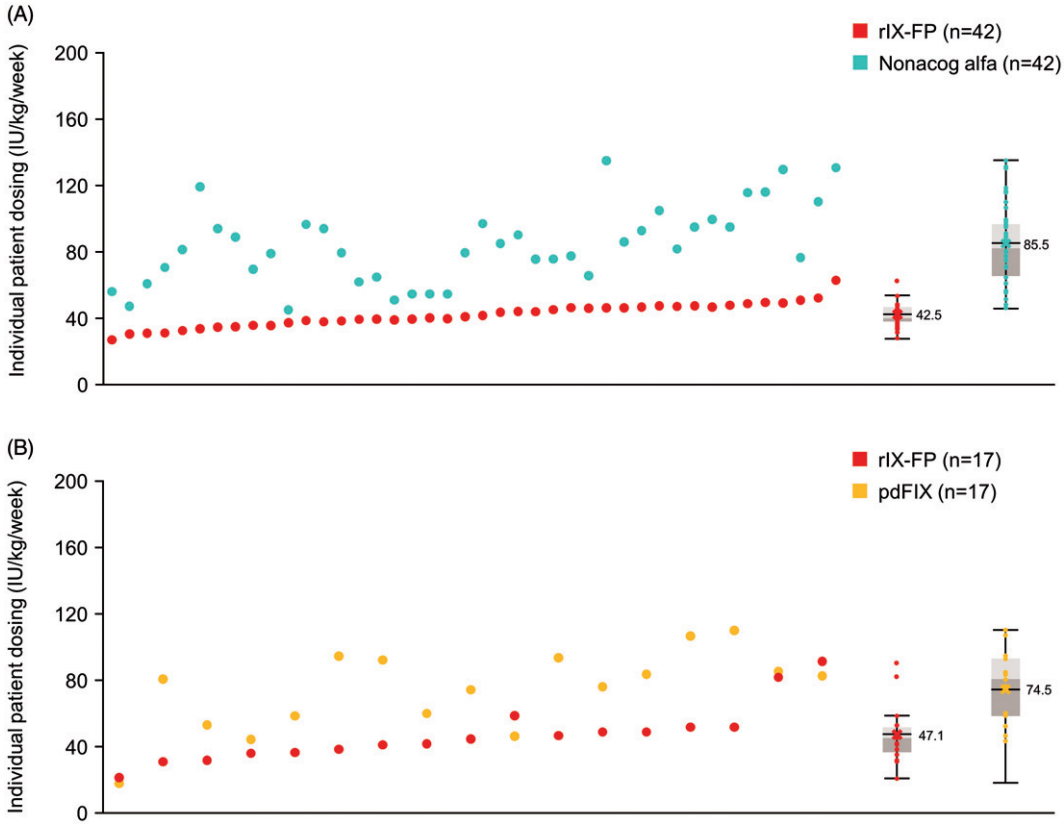

Figure 3. Intra-patient dosing for prophylaxis with rIX-FP and prior prophylaxis product (A) nonacog alfa or (B) pdFIX. Individual patient data are displayed on the x-axis. Dosing for each patient on rIX-FP is plotted in red; dosing on the prior product in the same patient is plotted vertically in blue (nonacog alfa, $n = 42$) or yellow (pdFIX, $n = 17$). X-mark and label indicate mean, whiskers indicate minimum and maximum values, dark grey zone indicates 2nd quartile range (25th–50th percentile), light grey zone indicates 3rd quartile (50th–75th percentile), boundary between grey zones indicates median. pdFIX, Plasma-derived factor IX.

of all pdFIX products was 83.5 IU/kg/wk ($n = 1$; range 83.5). Of note, differences between rIX-FP and prior treatment should be interpreted with caution in those patients aged 0–11 years due to the small sample size.

Figure 3 shows intra-patient comparison of replacement factor dosing in the prophylaxis-to-prophylaxis group ($n = 59$). All patients previously treated with nonacog alfa had lower weekly FIX consumption with rIX-FP compared to their prior drug ($n = 42$) (Figure 3(A)). Mean weekly consumption of rIX-FP in this group was 42.5 IU/kg/wk on rIX-FP, compared with 85.5 IU/kg/wk on nonacog alfa. In total, 14 out of 17 patients previously treated with pdFIX had lower FIX consumption with rIX-FP compared to their prior drug (Figure 3(B)). Mean weekly dose on pdFIX was 74.5 IU/kg/wk compared with 47.1 IU/kg/wk for the same patients treated with rIX-FP. Mean weekly dose with all prior products combined (nonacog alfa and pdFIX) was 82.3 IU/kg/wk, 88% more than on rIX-FP (43.8 IU/kg/wk) for the same patients ($n = 59$). When corresponding intra-patient comparisons were performed for all patients aged ≥12 years ($n = 53$) mean weekly consumption was 42.4 IU/kg/wk on rIX-FP, compared with 84.3 IU/kg/wk on nonacog alfa ($n = 37$); mean weekly dose on pdFIX was 74.0 IU/kg/wk compared with 44.4 IU/kg/wk for the same patients treated with rIX-FP ($n = 16$); mean weekly dose with all prior products combined (nonacog alfa and pdFIX) was 81.2 IU/kg/wk, 89% more than on rIX-FP (43.0 IU/kg/wk) for the same patients ($n = 53$). In turn, the corresponding results for patients aged 0–11 years were: mean weekly consumption was 43.2 IU/kg/wk on rIX-FP compared with 94.2 IU/kg/wk on nonacog alfa ($n = 5$); mean weekly dose on pdFIX was 83.5 IU/kg/wk compared with 90.9 IU/kg/wk for the same patient ($n = 1$) treated with rIX-FP; mean weekly dose with all prior products combined (nonacog alfa and pdFIX) was 92.4 IU/kg/wk compared with 51.1 IU/kg/wk on rIX-FP, for the same patients ($n = 6$). Again, results should be interpreted with caution in those patients aged 0–11 years due to the small sample size.

Discussion

In this study, we found mean factor consumption was reduced in patients treated with rIX-FP compared to prior FIX product. Furthermore, in those patients where bleed data were available, ABR decreased and the number of patients with zero bleeds increased with rIX-FP compared to prior FIX therapy.

In Germany, prior to the introduction of the two EHL products, rIX-FP and rFIXFc, only SHL or pd FIX products were available for the treatment of hemophilia B. To our knowledge, this is the first study that assesses real-world clinical benefits of the switch from SHL/pd FIX products to EHL FIX products. Other studies of real-world experience in hemophilia B have come from the US and have focused on cost analysis and not on clinical benefits.[13]

Due to their significant increases in half-life, EHL FIX therapies have the potential to improve treatment experience and outcomes for patients with hemophilia B. Less frequent infusions could increase adoption of prophylaxis and adherence to the prescribed treatment regimen, and higher trough levels between doses could improve bleed control[14]. As such, EHL FIX therapies also have the potential to improve the quality of life (QoL). Clinical trials have already demonstrated an improvement in the QoL of patients treated with EHL FIX products.[15,16] Additionally, improving QoL was reported as the most frequent reason to switch to an EHL product according to real-world data collected in Canada.[17]

Clinical trial experience with rIX-FP

In clinical trials, rIX-FP was evaluated in previously treated adult and pediatric patients with severe or moderately severe hemophilia B.[8,18] Median annualized spontaneous bleeding rate was 0.00 in both populations across all prophylaxis regimens (once every 7, 10 or 14 days in adults; once every 7 days in pediatric patients).[8,18] Median trough level was 20 IU/dL with weekly dosing and 12.4 IU/dL with 14-day dosing in adults.[8] In children, median trough level was 13.4 IU/dL with weekly dosing.[18] All adult prophylaxis patients started the trial on a once-weekly regimen and were allowed to switch to a 10-day or 14-day regimen after 26 weeks if they had not suffered any spontaneous bleeds in the prior 4 weeks. Overall, 28 patients (70%) switched to a lower-frequency regimen, including 21 (53%) who switched to a 14-day regimen.

Real-world outcomes – annualized bleeding rate

The present study demonstrated that the low bleeding rates seen in clinical trials with rIX-FP are realized in routine clinical practice. Of note, in prophylaxis patients for whom detailed bleeding data were available, ABR was 88% lower with rIX-FP (0.3 ± 0.6) compared to all prior therapies (2.6 ± 2.9). Furthermore, the percentage of patients with zero bleeds was more than three times higher (81 vs. 24%) with rIX-FP compared to all prior therapies. Results restricted to patients aged $\geq$12 years, who comprised the majority (90.5%) of the prophylaxis-to-prophylaxis group, were consistent with the overall results.

Real-world outcomes – dosing frequency and factor consumption

With SHL FIX replacement products, patients with hemophilia B receiving prophylaxis require infusions on average twice per week, due to the short half-life (15–24 hours) of these products. The need for frequent dosing results in reduced adherence in some prophylaxis patients,[6] reluctance to transition to prophylaxis for many on-demand patients who continue to suffer bleeds, lower quality of life as a result, and potential infections and thrombotic complications due to the use of central venous access devices required in patients with poor venous access, particularly young children.[19] A significant reduction in infusion frequency with newer EHL FIX products could potentially improve outcomes and quality of life in all these patient groups. In the present study, we found that of 60 adult patients receiving prophylaxis with rIX-FP, 7 (12%) were previously treated on-demand, suggesting that rIX-FP may represent a more attractive treatment option for those reluctant to be placed on prophylaxis with SHL products.

We also found that 88% of pediatric and 91% of adult prophylaxis patients infused once a week or less often with rIX-FP, compared with 0% in both patient groups with nonacog alfa. While the label of rIX-FP allows for infusions every two weeks, a relatively low proportion of patients (8% of pediatric, and 7% of adult patients) infused every two weeks or less often. It is possible that German physicians adopt a relatively conservative treatment paradigm that aims for higher trough levels in order to ensure better bleed control compared to SHL treatment. It is also possible that infusion frequencies will progressively decrease as German physicians gain more experience with rIX-FP.

Mean weekly consumption of replacement factor for the patients included in this analysis was approximately 46% percent lower with rIX-FP compared to all prior SHL products (44 IU/kg/wk and 82 IU/kg/wk, respectively). For prophylaxis patients who switched from nonacog alfa to rIX-FP, replacement factor consumption decreased by 50%, from 85.5 IU/kg/wk to 42.5 IU/kg/wk. Similar results were found when analyses were restricted to patients aged $\geq$12 years. Given the lower factor utilization, as well as the lower bleeding rates with rIX-FP reported in this study, it is possible that rIX-FP utilization could lead to cost effectiveness or cost savings compared to SHL products. As such, a separate pharmacoeconomic analysis to assess the clinical-economic value of rIX-FP would be of value.

Of note, unlike the US where rFIXFc was available for more than a year before rIX-FP, in Germany, both EHL products became available at the same time. Therefore, this study only evaluated switching from SHL products to rIX-FP, as in the observed data no patients were reported to have switched from rFIXFc to rIX-FP. As further data become available, it would be interesting to compare clinical outcomes in patients switching between EHL products.

Limitations of the analysis

Limitations of the current analysis include a small sample size, short period of assessment, lack of information about the location, severity, treatment and outcomes of bleeding events, and patient adherence data (for which true and accurate measurements are very difficult to obtain and are usually not available in retrospective studies). Furthermore, the analysis considers only patients who had switched to rIX-FP from a prior replacement product. Depending on treatment guidelines by different physicians or centers, these patients (and their clinical outcomes on their prior drug) may not be representative of the entire patient population. For instance, some physicians may prioritize adherent patients for switches to new products, while others may first transition patients not well controlled on their current therapy. Finally, the calculation of factor consumption was based on the most recent prescription of each product. However, only

a small number of patients changed dose and/or dosing frequency, which was most likely related to treatment optimization. As such, the last prescribed dose should reflect the stable dosing and therefore serve as a good estimate of factor consumption over time. Despite these potential limitations, the results presented here are consistent with experience derived from rIX-FP clinical trials and suggest a potential benefit of switching from SHL replacement factors to rIX-FP for improved bleed control while achieving a lower treatment burden.

Conclusion

Use of extended half-life rIX-FP was associated with substantial reductions in both bleeding rates and consumption of replacement factor compared to prior SHL therapies. Further research is needed to confirm treatment patterns and outcomes in a larger patient sample and with a longer observation time.

Transparency

Declaration of funding

This work was supported by CSL Behring.

Declaration of financial/other relationships

JO has received reimbursement for attending symposia/congresses, honoraria for speaking and/or consulting and funds for research from Bayer, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Shire and Swedish Orphan Biovitrum; SY is an employee at CSL Behring; GK was an employee at CSL Behring when this study was performed; GM is an employee of Adivo Associates; AT has received grants and personal fees for lectures and consultancy from Alnylam, Bayer, Biogen Idec, Biotest, Boehringer Ingelheim, Chugai, CSL Behring, Daiichi Sankyo, Leo Pharma, Novo Nordisk, Octapharma, Pfizer, Portola, Roche, Shire, and SOBI. A reviewer on this manuscript has disclosed being an investigator on a study funded by CSL Behring. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Author contributions

GK and SY contributed to the conception, design and analysis of the study. GM provided substantial contributions to the data collection and analysis and drafting the manuscript. JO and AT were integral to reviewing the manuscript for important intellectual content. All authors gave final approval of the version to be published.

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Data availability

CSL will only consider requests to share Individual Patient Data (IPD) that are received from systematic review groups or bona-fide researchers. CSL will not process or act on IPD requests until 12 months after article publication on a public website. An IPD request will not be considered by CSL unless the proposed research question seeks to answer a significant and unknown medical science or patient care question. Applicable country specific privacy and other laws and regulations will be considered and may prevent sharing of IPD.

Requests for use of the IPD will be reviewed by an internal CSL review committee. If the request is approved, and the researcher agrees to the applicable terms and conditions in a data sharing agreement, IPD that has been appropriately anonymized will be made available. Supporting documents including study protocol and Statistical Analysis Plan will also be provided.

For information on the process and requirements for submitting a voluntary data sharing request for IPD, please contact CSL at clinicaltrials@cslbehring.com.

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