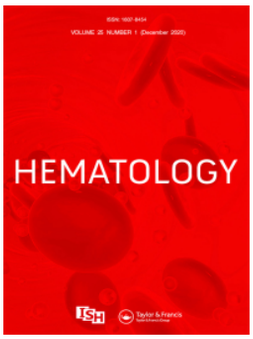

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CASE REPORT

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Benefits of rIX-FP prophylaxis in patients with Haemophilia B: real-world evidence from a Spanish reference centre

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ABSTRACT

Standard FIX prophylaxis for PWHB require frequent injections, which has led to the development of extended half-life products like rIX-FP (albutrepenonacog alfa) that has shown good efficacy in clinical studies. This ambispective study aims to report a real-world experience with rIX-FP in a Spanish centre with PWHB who switched from SHL-FIX or began prophylaxis with rIX-FP. Five PWHB were included in this study, Four PTP switched to rIX-FP with prophylaxis every 7 days whilst one PUP started with an every-14-days regimen. 3 PTPs extended their dosing intervals to every 14 days or every 21 days. In all PTPs, median annualized spontaneous and joint bleeding rates were maintained at 0.00 and median (range) of ABR was 0.92 (0.00–2.77) after switch to rIX-FP. Mean trough level with previous product was 3.68% ($SD = 2.06$), while it was 7.08% ($SD = 3$) with all rIX-FP dosing intervals. After switching to rIX-FP, all PTP reduced their annual infusion rate between 50 and 84% and their annual FIX consumption by 61% (59–67%). This is the first reported real-world experience with albutrepenonacog alfa in a small cohort in Spain and demonstrates good bleeding control together with a reduction of the infusion rate, factor consumption and higher through factor level than previous treatment.

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Introduction

Haemophilia B, caused by a deficit or defective functioning of clotting factor IX (FIX), entails significant morbidity and socioeconomic effects [1,2]. The most characteristic signs of the severe forms of the disease are recurrent bleeds into deep tissues and joints that may cause disabilities, chronic pain, poor quality of life (QoL) and even early death [1]. The conventional treatment of haemophilia B patients focuses on replacing the FIX with plasma-derived or recombinant FIX (rFIX) concentrates either on-demand (in the presence of bleeding events) or prophylactically (with regular infusions) [3]. Among these options, primary prophylaxis has become the standard of care for haemophilia patients, demonstrating a reduced morbidity, improved QoL and longer life expectancy [4–6]. Despite the advantages of early onset with prophylactic treatment, there are still some unmet needs. The risk of inhibitor development on the onset of treatment or after the replacement product switch, and the frequent need of intravenous injections (2-3 times per week) due to the short plasma half-life with standard products poses the main burden for the patients and directly impacts on treatment adherence and patient´s QoL [7]. Therefore, the objective in the last years has been to develop clotting factors with longer plasma half-lives (extended half-life rFIX [EHL-rFIX]), to considerably expand the administration intervals up to 7–14 days or even 21 days [8]. One of these new products, rIX-FP (albutrepenonacog alfa), is a recombinant fusion protein that genetically links human FIX with human albumin. It has been proven how it significantly enhances the pharmacokinetic (PK) profile, which translates into long-lasting efficacy and therefore a decreased infusion frequency [9,10].

Despite the evidence derived from clinical trials and epidemiological studies, more real-world data are needed to better understand the impact of prophylactic regimens with EHL-rFIX products on the therapeutic outcomes in patients with haemophilia B (PWHB). Thus, the aim of this work was to report a real-world experience on managing rIX-FP prophylaxis in a Spanish reference centre.

Materials and methods

This real-world ambispective study included PWHB from a reference Spanish centre (Hospital Vall d´Hebron, Barcelona, Spain) who were either treated with standard half-life FIX (SHL-FIX) on a prophylaxis

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regimen and switched to rIX-FP or were previously untreated and began prophylaxis with rIX-FP. Sociodemographic, clinical and treatment outcome data were collected from medical records for 12 months prior to the switch or treatment start with rIX-FP and for the next 12 months. These included age, body weight, infusion frequency and dose, annualized bleeding rates (ABR), annualized joint bleeding rates (AjBR), annualized spontaneous bleeding rates (AsBR), haemophilia early arthropathy detection with ultrasound (HEAD-US) score, number of annual infusions, and factor consumption. Additionally, a pharmacokinetic analysis was conducted via the WAPPS-Hemo platform to assess trough FIX levels and FIX levels after 48 h, 5 and 7 days with rIX-FP.

Descriptive summary statistics (mean, median, standard deviation [*SD*]) were applied for the following baseline characteristics and variables: age, previous FIX trough level analyzed after longest period, previous ABR, previous AjBR, previous number of annual infusions, previous annual factor consumption per kg during prophylaxis (IU), FIX through level with rIX-FP, ABR with rIX-FP, AjBR with rIX-FP, and annual factor consumption per kg during prophylaxis (IU) with rIX-FP. FIX through level were determinated by a mean values from a repetitive blood sampling, in both treatments.

The study was reviewed and approved by the Ethics Committee of our hospital with code EOM(AG)028/2021(5826) and adheres to the principles of the Declaration of Helsinki.

Results

Five patients with severe haemophilia B, with a mean age of 25 years (range 1–60 years), were included in the study. Four of them, three adult patients and one paediatric patient, had been previously treated with SHL-FIX products (three recombinant and one plasma-derived FIX) on a 2 times per week prophylaxis regimen. The reason for switching patients, who were already on prophylaxis, was to reduce the number of infusions to improve their quality of life.

The other patient was one year old and had not been previously treated.

Data collected from the 12 months prior to the switch to rIX-FP and comparison with the same variables after the switch are shown in Tables 1 and 2. Four PTP patients began prophylaxis with rIX-FP (albutrepenonacog alfa) every 7 days for at least one month before considering treatment individualization, and one patient started an every-14-days regimen. The treatment was adjusted based on clinical considerations, individualized PK profile and patient needs (bleeding phenotype, physical activity). Adjustments were first performed to infusions every 14 days and lately to infusions every 21 days based on the same evaluation criteria [11]. Thus, the treatment regimens for the 4 PTP patients were adjusted for three of them, one adult switched to every 14 days dosing frequency, while the other two previously treated adults were able to further extend dosing to every 21 days. PUP patient started with rIX-FP prophylaxis with a dose of 30 IU/kg every 14 days and FIX trough level was 1.7%. The decision to start every 14 days was the bad venous access. In order to increase his FIX trough level, the patients was assigned to a prophylaxis regimen of 50 IU/kg every 14 days. After 61 infusions, the patient had no inhibitors, and had maintained a FIX trough level of 3.7% with an annualized spontaneous and joint bleeding rates (AsBR and AjBR) of 0 (Table 1). In all PTPs, median AsBR and AjBR were maintained 0.00 and median (range) of ABR was 0.46 (0.00–2.77) after switch to rIX-FP. All bleeding rates for the previously untreated patient (PUP) after one year with rIX-FP were also 0.0).

In PTPs, mean trough levels with a twice per week SHL-FIX product was 3.68% ($SD = 2.06$), while it was 7.08% ($SD = 3$) with all dosing intervals during rIX-FP treatment with and improvement on the majority of PTP patients on FIX trough level. In addition, predicted mean FIX level at day 7 post-infusion according to WAPPS-Hemo was 19.82% ($SD = 6$) for these patients (Table 3). The lowest FIX level at day 7 post-infusion was detected in the paediatric patient receiving prophylaxis every 7 days. According to the obtained individual PK profile with WAPPS-Hemo, the half-life of rIX-FP was more than 110 h for four patients, reaching the highest value of 181 h (data not shown). Interestingly, the half-life was much lower for the two paediatric patients (50 h in the youngest and 111 h in the eldest) compared to the adults. The individual WAPPS-Hemo PK profile was available only for one of the formerly administered SHL-FIX products with a half-life of the SHL-FIX of 41.5 h (data not shown).

The number of annual infusions decreased for all PTP after switching to rIX-FP (Table 1), and the most significant difference was achieved in patients on every 21 days regimen (104 versus 17 annual infusions). Thus, the annual infusion rate was reduced 50% in one patient, 75% in another patient, and 84% in the remaining two. Regarding factor consumption, the mean value of administered IU during a 12-month prophylaxis went from 188500 ($SD = 102637$) to 71850 ($SD = 4378$). Therefore, patients reduced their annual FIX consumption by 61% (59–67%) from 4287 ± 1044 IU/kg/year with SHL-FIX products to 1658 ± 510 IU/kg/year with rIX-FP. Overall adherence rates in our real practice patient series was 100% for the first year with rIX-FP. Finally, there were no reported adverse events following initiation or switch to rIX-FP.

Table 1. Baseline characteristics and treatment outcomes before and after the start or switch to rIX-FP in the included patients.

		Previous treatment with SHL-FIX						Treatment with rIX-FP (albutrepenonacog alfa)						
Patient	Age	Prophylactic regimen	FIX trough level (%)	ABR[Ŧ]	AsBR	AjBR	Number of annual infusions	Factor consumption (IU/kg/year)	Prophylactic regimen	FIX trough level[b]	ABR[Ŧ]	AsBR	AjBR	Number of annual infusions	Factor consumption (IU/kg/year)
1	32	33 IU/kg Twice per week Recombinant FIX	2.4	0	0	0	104	3441	65 IU/kg Every 21 days	6.1	0.92	0	0	17	1147
2	7	55 IU/kg Twice per week Recombinant FIX	3	0	0	0	104	5777	45 IU/kg Every 7 days	11.3	0.92	0	0	52	2363
3	23	35 IU/kg Twice per week Recombinant FIX	3.6	0.6	0	0.6	104	3714	55 IU/kg Every 14 days	6.9	0	0	0	26	1516
4	60	40 IU/kg Twice per week Plasma-derived FIX	5.7	0	0	0	104	4216	95 IU/kg Every 21 days	5.9	1.85	0	0	17	1606
5[a]	1	N/A		N/A	N/A	N/A	N/A	N/A	20 IU/kg Every 14 days	1.7	0	0	0	26	520

ABR, annualized bleeding rate; AsBR, annualized spontaneous bleeding rate; AjBR, annualized joint bleeding rate; IU, international units; N/A, not applicable; SHL, standard half-life.
[a]Previously untreated paediatric patient.
[b]Trough level at 7, 14 and 21 days according each patient.

Table 2. Joint status before and after the start or switch to rIX-FP in the included patients.

Patient code	Pre-switch HEAD-US (score total)	Post-switch HEAD-US (score total)
P1	1	0
P2	3	2
P3	4	2
P4	17	17
P5	NA	0

Table 3. Trough level at 7 days.

Patient code	FIX trough level at 7 days
P1	24.3
P2	11.3
P3	20.6
P4	23.1
P5	1.7

Discussion/conclusion

This is the first analysis to assess the real-world clinical benefits of switching to prophylaxis with rIX-FP from a prior SHL product in Spain. Actually, there are still limited real-world data with albutrepenonacog alfa, however, these data are consistent throughout all studies and Real-world data [8,12–15]. An expert opinion article comparing different available factor IX products, based on a literature review and their expertise, positioned rIX-FP as an effective and safe option for the prophylactic treatment of PWHB of all ages [11]. Besides, the experts threw recommendations in terms of dosing, regimens, and management of the treatment switch to rIX-FP. Our study presents some obvious limitations, such as the small sample size or the lack of certain retrospective data for some patients. Nevertheless, it is important to have data about the real-world use of rIX-FP in various settings and populations and this study reports real practice experience with rIX-FP in Spain after a single case report published with concordant results [16].

ABR results shown are in alignment with data from clinical trials, corroborating that rIX-FP provides an effective haemostasis both in PTP and PUP with moderately severe to severe haemophilia B at dose regimens of up to 14 or 21 days [12]. In our serie, the ABR increased after switching to EHL could be explained because the patients increased their physical activity and the bleeding were traumas. However, AsBR and AjBR remained at 0. Patients have shown a reduced infusion frequency and FIX IU consumption following the switch to prophylaxis with rIX-FP, from infusions every 3,5 days (twice a week) on previous SHL product to once a week or up to every 21 days after switch. This reduction on infusion frequency implies a reduction on annual FIX consumption between 59% up to 67%. Reduced dosing frequency may improve treatment adherence and has the potential to improve treatment experience by reducing treatment burden [17], although our cohort were highly adherent with the previous treatment, extension infusion frequency with rIX-FP has not impacted on their adherence and in line with overall adherence rates (defined as receiving 10% of the prescribed dose 80% of the time) of 95.5% and 92% reported in clinical and real-world studies with rIX-FP, respectively, with all dose regimens in adult/adolescent patients. Furthermore, it was 98% in paediatric patients for a 7-day regimen [18]. It is well known that patient adherence with prophylaxis regimens is essential for preventing bleeds in PWHB.

The higher trough levels achieved with rIX-FP, also with extended infusion frequency, compared with twice a week prophylaxis with previous SHL were in line with published data [19] and it may give an additional potential to improve patient management and could allow the patient to live a more active lifestyle [20]. While treatment efficacy should always remain the most important outcome when selecting a treatment regimen, the enhanced features of rIX-FP are allowing patients with haemophilia the opportunity to live a healthier and less burdensome life [17].

In conclusion, this is the first real-world cohort experience with rIX-FP reported from a Spanish centre. The results demonstrate that PWHB who switched to rIX-FP from a SHL-FIX were able to reduce their infusion rate and factor consumption, while maintaining good bleed control and increasing their FIX trough level and these could have an impact on their treatment burden and quality of life.

Disclosure statement

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