

Cross-sectional epidemiological study to understand the approach to treatment in the routine care of patients with hemophilia B in Spain and Portugal

Estudio epidemiológico transversal para comprender el abordaje del tratamiento en la atención habitual de pacientes con hemofilia B en España y Portugal

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Abstract

Introduction: Treatment options for patients with hemophilia B (PWHB) have improved in the last decade, but epidemiological studies are required to optimize clinical management and define unmet needs. **Objective:** The objective of the study is to investigate current disease management and quality of life (QoL) in PWHB in Spain and Portugal. **Methods:** Epidemiological, cross-sectional, multicenter study with moderately severe and severe PWHB. Sociodemographic, epidemiological, clinical, treatment, and QoL data were collected retrospectively over a 24-month period. **Results:** Of the 75 patients included in the study, 78.7% received prophylactic treatment and 21.3% on demand; 65.3% were treated with SHL-FIX and 10.7% with rIX-FP. Bleeding occurred in 81.3%, mainly in the form of spontaneous bleeding. Prophylaxis resulted in a lower annualized bleeding rate, better joint health, and better QoL, compared to on-demand treatments. Patients treated with rIX-FP throughout the study had better disease control and QoL than those treated with SHL-FIX. **Conclusion:** With the largest sample to date of PWHB from Spain and Portugal, our understanding of the management and impact of hemophilia B is broadened and, in accordance with previous evidence, it shows the benefits of prophylaxis and the advantages that the FIX extended half life products life FIX can offer.

Keywords: Hemophilia B. Spain. Portugal. Epidemiologic studies. Treatment outcome. Quality of life.

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Resumen

Introducción: Los tratamientos para la hemofilia B (HB) han mejorado en la última década, pero se requieren estudios para optimizar el manejo clínico e identificar las necesidades no cubiertas. **Objetivo:** Investigar el manejo de la enfermedad y la calidad de vida (CdV) en España y Portugal. **Métodos:** Estudio epidemiológico, transversal, multicéntrico, que incluye pacientes con HB grave y moderadamente grave. Datos sociodemográficos, epidemiológicos, clínicos, de tratamiento y de CdV se recopilaban retrospectivamente durante un período de 24 meses. **Resultados:** 75 pacientes incluidos, el 78,7% recibieron tratamiento profiláctico y el 21,3% a demanda; el 65,3% tratados con SHL-FIX y un 10,7% con rIX-FP. El sangrado ocurrió en el 81,3%, principalmente sangrados espontáneos. La profilaxis dio como resultado ABR más bajas, mejor salud articular y mejor CdV, en comparación con los tratamientos a demanda. Los pacientes tratados con rIX-FP durante todo el período de estudio presentaron mejoras en el control de la patología y la CdV que los tratados con SHL-FIX. **Conclusión:** Con la muestra más amplia hasta la fecha de HB de España y Portugal se amplía nuestra comprensión de la hemofilia B y, en concordancia con la evidencia previa, muestra los beneficios de la profilaxis y las ventajas que los EHL-FIX pueden ofrecer.

Palabras clave: Hemofilia B. España. Portugal. Estudios epidemiológicos. Resultado del tratamiento. Calidad de vida.

Introduction

Hemophilia B is a recessive, X-linked congenital hemorrhagic disorder caused by a deficit or defective functioning of clotting factor IX (FIX)¹. Prevalence (per 100 000 males) is 3.8 cases for all severities of hemophilia B, and 1.1 cases for severe hemophilia B (i.e., < 1% of normal FIX coagulant activity, FIX: C)². Hemophilia B is estimated to account for 15-20% of the total hemophilic population³. Despite its low incidence, the morbidity and socioeconomic effects associated with the disease are significant. The untreated severe forms of hemophilia B are characterized by recurrent spontaneous bleeds into deep tissues and joints that result in chronic pain, severe disabilities, and early death⁴. Severe hemophilia B is diagnosed very early, usually before 2 years of age. However, in recent years, due to increased awareness and improved recognition, more than half of cases are diagnosed in the neonatal period^{5,6}.

Current treatment for hemophilia B consists of replacing the absent or defective coagulation factor, either when bleeding events occur (on-demand treatment) or by regularly scheduled infusions (prophylactic treatment) with plasma-derived or recombinant FIX concentrates⁷. Based on evidence from clinical trials, primary prophylaxis of bleeding episodes has become the unquestionable standard of care for these patients^{8,9}. The emergence of high-quality replacement therapies with recombinant factors and advances in the management of bloodborne viral infections have led to reduced morbidity, improved quality of life (QoL), and patient life expectancy close to that of the general male population^{7,10}. Nevertheless, these therapeutic options present some obstacles, including suboptimal patient compliance, particularly in children and adolescents, due to the need for frequent intravenous injections (plasma

half-life of replaced FIX ranges from 18 to 22 h), as well as high costs and other potential problems such as the development of inhibitors^{11,12}.

Attempts have been made in the last decade to develop clotting factors with longer plasma half-lives, enabling the frequency of intravenous injections to be reduced from 2-3 times/week to once every 7-14 or even 21 days¹³. Together with gene therapy, these are promising therapeutic options for hemophilia B patients^{14,15}. The new extended half-life rFIX (EHL-rFIX) products have resulted in a reduction in annual infusions and better protection of patients by modification of rFIX with its fusion to the immunoglobulin G (IgG) Fc domain or recombinant albumin, or by the addition of polyethylene glycol to the rFIX. rIX-FP (albutrepenonacog alfa) is a recombinant fusion protein genetically linking human coagulation FIX with human albumin. It was engineered to significantly enhance the pharmacokinetic profile and provide long-lasting hemostatic efficacy of FIX to allow for less frequent dosing in hemophilia B treatment¹⁶.

Epidemiological studies are needed to better understand and optimize the clinical management of hemophilia B patients. Herein, we report the results of a multicenter cross-sectional epidemiological study aimed at improving our understanding of the current management and care of patients with hemophilia B in routine clinical practice in Spain and Portugal, describing the therapeutic strategies used and their impact on the QoL of these patients.

Methods

Study design

This was a non-interventional, observational, cross-sectional, multicenter study in both pediatric and adult

patients with hemophilia B. The study was conducted at 12 sites in Spain (n = 7) and Portugal (n = 5). The primary purpose was to describe the management and treatment of patients with hemophilia B within routine clinical practice in Spain and Portugal and to assess their impact on the QoL of these patients. The protocol was reviewed and approved by the Institutional Review Board at each study site (study code: IIS-2017-12-04) and the study was conducted according to the principles of Good Pharmacovigilance Practices (GVP) and the Declaration of Helsinki. All patients provided written informed consent before entering the study.

Study population

Eligible patients had moderately severe-to-severe hemophilia B ($\leq 2\%$ of normal FIX coagulant activity, FIX: C), were receiving prophylactic or on-demand treatment, and were able to answer a self-administered questionnaire (or a guardian in the case of children). Patients were excluded if they were participating in a clinical trial or had known hypersensitivity to any of the FIX products or hamster protein.

Information retrieval

Eligible patients or their parents/care given were asked to sign an Informed Consent form and complete the EQ-5D-5L questionnaire, including a Visual Analog Scale (VAS), during a routine visit. Clinical data from the previous 2 years were retrospectively collected from patient medical records using an electronic data capture system (EDC). Sociodemographic, epidemiological, clinical, and treatment outcome data were recorded. Study variables included: annualized bleeding rates (total, spontaneous, and traumatic) during on-demand and prophylactic treatment, number of spontaneous bleeding episodes per patient, number of infusions (and doses) required to treat bleeding episodes, assessment of hemostatic efficacy in the treatment of bleeding episodes, treatment patterns (on-demand and prophylaxis), dosage, factor consumption, frequency of infusion, change in dosing frequency, location of bleeds, joint status (if available), number of patients who developed FIX inhibitors, nature and incidence of adverse reactions, laboratory parameters, and EQ-5D5L QoL.

Statistical analysis

Descriptive statistics were used to describe variables. Quantitative variables were described as mean,

median, standard deviation (SD), minimum, maximum, interquartile range (IQR), and number of patients. Qualitative variables were described by their absolute and relative frequency distribution. An overall analysis was performed including all patients and, additionally, an independent analysis was carried out for children and adolescents/adults. Derived variables included body mass index (BMI, kg/m^2), BMI stratification, age group at hemophilia B diagnosis, time (years) since hemophilia B diagnosis, FIX trough level, FIX peak level, time (months) since the most recent inhibitor test, Hemophilia Joint Health Score (HJHS), duration (days) of adverse event, annualized bleeding rate (ABR), annualized spontaneous bleeding rate (AsBR), annualized joint bleeding rate (AjBR), and annualized traumatic bleeding rate (AtBR). Subgroup analyses were performed according to age (children under 12 vs. adolescents/adults over 12 years) and treatment regimen (prophylaxis vs. on-demand). All statistical analyses were based on the available data with no imputation of missing data, except for missing dates. Statistical analyses were carried out using the SAS v9.3 statistical package (SAS Institute Inc., Cary, NC, USA).

Results

Patient demographic and disease characteristics

From September 2018 to August 2019, a total of 75 eligible patients (12 children ≤ 12 years old and 63 adolescents/adults, > 12 years) with moderately severe-to-severe hemophilia B ($\leq 2\%$ of normal FIX coagulant activity, FIX: C) were enrolled. Patient baseline demographic and disease characteristics are summarized in [table 1](#) and [table S1](#). All patients were male, with a median age of 5 years (IQR = 4-8) for children and 31 years (IQR = 22-46) for adolescents/adults. BMI was calculated for 18-year-old patients or older (n = 38); the median BMI of these patients was 24.1 kg/m^2 (IQR = 22.5-28.7). The median time from diagnosis of hemophilia B was 4.5 years (IQR = 4.0-7.5) for children and 26 years (IQR = 17.0-38.0) for adolescents/adults, with the majority of patients having been diagnosed during childhood (< 6 years). About 40% of patients had a family history of hemophilia B. Most children (91.7%) and more than half of adolescents/adults (67.7%) had no concomitant diseases. The most frequent concomitant conditions were cardiovascular disease (14.5%) and viral infection (HCV 12.9%, and HIV 9.7%) among adolescents/adults, and other clotting disorders (8.3%)

Table 1. Patient baseline demographic and disease characteristics

Characteristic	All (n = 75)	Children* (n = 12)	Adolescents/adults (n = 63)
Male sex - No. (%)	75 (100.0)	12 (100.0)	63 (100.0)
Age - yrs			
Mean $\pm$ SD	29.4 $\pm$ 17.9	5.9 $\pm$ 2.6	33.9 $\pm$ 16.0
Median (IQR)	29 (14-41)	5 (4-8)	31 (22-46)
BMI - kg/m ^{2†}			
Mean $\pm$ SD	-	-	25.8 $\pm$ 5.8
Median (IQR)	-	-	24.1 (22.5-28.7)
Time from HB diagnosis - yrs			
Mean $\pm$ SD	23.1 $\pm$ 15.4	5.5 $\pm$ 2.2	28.2 $\pm$ 13.8
Median (IQR)	21 (11.0-33.0)	4.5 (4.0-7.5)	26 (17.0-38.0)
Treatment regimen - No. (%)			
On demand	16 (21.3)	1 (8.3)	15 (23.8)
Prophylaxis	59 (78.7)	11 (91.7)	48 (76.2)
Surgeries during the study period - No. (%)			
Not known	4 (5.3)	0 (0.0)	4 (6.3)
No	57 (76.0)	10 (83.3)	47 (74.6)
Yes	14 (18.7)	2 (16.7)	12 (19.0)
Hemostatic efficacy during surgery - No. (%)			
Excellent	8 (57.1)	1 (50.0)	7 (58.3)
Good	4 (28.6)	1 (50.0)	3 (25.0)
Not known	2 (14.3)	0 (0.0)	2 (16.7)

*Patients < 12 years old.

†BMI calculation only established for adolescents/adults $\geq$ 18 years (missing data, n = 14).

BMI: body mass index; HB: hemophilia B; IQR: interquartile range; No.: number; SD: standard deviation; yrs: years.

among children (data not shown). Most patients (78.7%) were treated with a prophylactic regimen (91.7% of children and 76.2% of adolescents/adults). In total, 14 patients underwent 22 surgeries; 2 children (16.7%) and 12 adolescents/adults (19.0%) had at least one surgery within the 24 months before enrollment. Eight patients had undergone one surgery (one patient - prostate biopsy, two patients - knee replacement, one patient - port-a-cath implantation, one patient - dental care, two patients - tooth extraction, and one patient - left ankle replacement), four patients had undergone two surgeries (one patient two dental extractions; one patient dental extraction and dental implant; one patient fracture of the right femur and extraction of four teeth; and one patient septoplasty and viscosupplementation of the left knee), and two patients had undergone up to three surgeries (one patient two knee injections and one tooth extraction; and one patient three left ankle synoviorrhesis). Short-term prophylaxis was used during all surgeries, with good or excellent hemostatic outcomes in all patients for whom the result was available (n = 12).

Two patients receiving prophylaxis (3.6%) had a previous history of FIX inhibitors: one patient had a low

inhibitor titer (0.62 BU/mL according to the Nijmegen method) that resolved spontaneously; the other patient had a high inhibitor titer (> 16 BU/mL) that was successfully eradicated by immune tolerance induction with plasma-derived clotting FIX concentrate before entering the study.

Treatments

Overall, 59 patients (78.7%) received prophylactic treatment and 16 (21.3%), on-demand treatment. Eleven out of the twelve children (91.7%) were on prophylactic treatment, and one was treated on demand. In the case of adolescents/adults, 48 of the 63 patients (76.2%) were on prophylactic treatment and 15 (23.8%) had treatment on demand. Almost all children (n = 11, 91.7%) had been treated with recombinant factors at some point during the study period, while only one child (8.3%) received treatment with plasma-derived factor during the study. Two children who were previously on treatment with standard half-life recombinant factors (SHL-rFIX) switched prophylaxis treatment to rIX-FP (albutrepenonacog alfa) (one child was on SHL-rFIX 2000 IU twice a week and switched to albutrepenonacog

Table 2. Treatment received according to age and treatment regimen

Treatment - No. (%)	Children (n = 12)		Adolescents/adults (n = 63)	
	On demand (n = 1)	Prophylaxis (n = 11)	On demand (n = 15)	Prophylaxis (n = 48)
Albutrepenonacog alfa	0 (0.0)	0 (0.0)	0 (0.0)	6 (12.5)
Plasma-derived FIX (pd-SHL)	0 (0.0)	1 (9.1)	6 (40.0)	13 (27.1)
pd-SHL to SHL-recombinant*	0 (0.0)	1 (9.1)	1 (6.7)	0 (0.0)
SHL-recombinant	1 (100.0)	7 (63.6)	8 (53.3)	29 (60.4)
SHL-recombinant to albutrepenonacog alfa*	0 (0.0)	2 (18.2)	0 (0.0)	0 (0.0)

*Patients who switched treatment over the study period from plasma derived FIX to recombinant FIX-SHL or from recombinant FIX-SHL to recombinant FIX-EHL (rIX-FP/albutrepenonacog alfa).

alfa 2000 IU q10 day, and the other was on SHL-rFIX 2000 IU weekly and switched to albutrepenonacog alfa 2000 IU every 3 weeks). In the case of adolescents/adults, 38 (60.3%) had been treated with recombinant factors at some point, 19 (30.2%) with plasma factor and six (9.5%) with albutrepenonacog alfa (all of them received it as prophylaxis) (Table 2). Almost three-quarters of adult patients, 71.4%, reported self-administration of treatment (data not shown). The median patient consumption per week over the last prophylactic dose regimen with albutrepenonacog alfa was 27.5 IU/kg (IQR = 25.3-29.8) in children and 34.7 IU/kg (IQR = 32.2-41.8) in adults. The median weekly consumption of plasma-derived factors was 87.0 IU/kg (IQR = 74.1-100) and 41.4 IU/kg (IQR = 38.5-44.4) in children and adults, respectively, while for recombinant factors this was 61.0 IU/kg (IQR = 55.2-62.5) in children and 65.0 IU/kg (IQR = 37.0-93.8) in adults.

Bleeding

ANNUALIZED BLEEDING RATES

The overall median ABR was 2.5 (IQR = 0.5-8.0) for patients with on-demand treatment (0.0 in children and 2.5 in adolescents/adults) and 1.0 (IQR = 0.5-2.0) for patients receiving prophylactic treatment (1.0 in children and 0.5 in adolescents/adults). The median AsBR was 1.0 (IQR = 0.0-5.5) for patients with on-demand treatment (0.0 in children and 1.8 in adolescents/adults) and 0.0 (IQR = 0.0-0.5) for patients with prophylactic treatment (0.0 in both children and adolescents/adults); median AjBR was 1.0 (IQR = 0.0-5.5) for patients with on-demand treatment (0.0 in children and 1.8 in adolescents/adults) and 0.5 (IQR = 0.0-1.0) for patients on prophylactic

treatment (0.5 in both children and adolescents/adults); and median AtBR was 0.0 (IQR = 0.0-1.0) for patients with on-demand treatment (0.0 in children and 0.3 in adolescents/adults) and 0.3 (IQR = 0.0-1.0) for patients on prophylactic treatment (1.0 in children and 0.0 in adolescents/adults). Nine adolescents/adults receiving on-demand treatment and five receiving prophylaxis had target joints. Among children, two patients on a prophylactic regimen had target joints (data unknown for one patient) (Table 3, see details on outlier treatment).

Number and type of bleeds

The majority of patients had bleeds, mostly spontaneous or joint bleeds. A total of 508 bleeds were recorded in 61 patients (81.3%), of whom nine were children (75%, 37 bleeds) and 52 adolescents/adults (82.5%, 355 bleeds). All the children who had bleeds were on prophylactic treatment; only one pediatric patient was treated on demand and had no bleeds reported. In adolescents/adults, 116 of 508 bleeds (22.8%) occurred in patients who were treated on demand (n = 10) and 392 (77.2%) in patients who were on prophylactic treatment (n = 51), although three adolescent/adult patients on prophylaxis were accountable for 192 bleeds (outlier patients mentioned on table 3). Of these 508 bleeds, 317 (8 in children and 309 in adolescents/adults) were spontaneous (239 on prophylaxis and 78 on on-demand treatment), 284 (17 in children and 267 in adolescents/adults) were joint bleeds (215 on prophylaxis and 69 on on-demand treatment), and 85 (29 in children and 56 in adolescents/adults) were traumatic bleeds (68 on prophylaxis and 17 on on-demand treatment) (Table S2).

Table 3. Annualized bleeding rate according to age, type of bleeding, and treatment regimen

Annualized bleeding rates	Total		Adolescents/adults		Children*
	On demand	Prophylaxis	On demand	Prophylaxis	Prophylaxis
ABR	n = 16	n = 56 [†]	n = 15	n = 45 [†]	n = 11
Mean ± SD	4.2 ± 4.5	1.6 ± 2.3	4.5 ± 4.5	1.6 ± 2.4	1.7 ± 1.8
Median (IQR)	2.5 (0.5-8.0)	1.0 (0.5-2.0)	2.5 (0.5-10.0)	0.5 (0.5-2.0)	1.0 (0.5-3.0)
Max-min	0.0-12.0	0.0-12.0	0.0-12.0	0.0-12.0	0.0-6.0
AsBR	n = 15 [‡]	n = 54 ^{§,¶}	n = 14 [‡]	n = 43 [¶]	n = 11
Mean ± SD	3.1 ± 3.8	0.7 ± 1.7	3.3 ± 3.8	0.8 ± 1.9	0.4 ± 0.6
Median (IQR)	1.0 (0.0-5.5)	0.0 (0.0-0.5)	1.8 (0.5-5.5)	0.0 (0.0-0.5)	0.0 (0.0-1.0)
Max-min	0.0-10.5	0.0-11.0	0.0-10.5	0.0-11.0	0.0-1.5
AjBR	n = 15 ^{**}	n = 56 ^{††,‡‡}	n = 14 ^{**}	n = 45 ^{‡‡}	n = 11
Mean ± SD	2.8 ± 3.4	0.9 ± 1.7	3.0 ± 3.4	1.0 ± 1.9	0.8 ± 1.1
Median (IQR)	1.0 (0.0-5.5)	0.5 (0.0-1.0)	1.8 (0.5-5.5)	0.5 (0.0-1.0)	0.5 (0.0-1.0)
Max-min	0.0-10.5	0.0-11.0	0.0-10.5	0.0-11.0	0.0-4.0
AtBR	n = 15 ^{§§}	n = 52 ^{§§}	n = 14	n = 41	n = 11
Mean ± SD	0.6 ± 0.8	0.7 ± 1.0	0.6 ± 0.8	0.5 ± 0.6	1.3 ± 1.6
Median (IQR)	0.0 (0.0-1.0)	0.3 (0.0-1.0)	0.3 (0.0-1.0)	0.0 (0.0-1.0)	1.0 (0.0-3.0)
Max-min	0.0-2.0	0.0-4.5	0.0-2.0	0.0-2.0	0.0-4.5

*Only one pediatric patient was treated on demand and had no bleeds reported.

[†]Three outliers from the adolescent/adult population in the prophylaxis group were removed (two patients with 48 bleeds and one patient with 96 bleeds).

[‡]No data available for the total number of spontaneous bleeds for one adult.

[§]No data available for the total number of spontaneous bleeds for three adolescents/adults.

[¶]Two outliers from the adult population in the prophylaxis group were removed (one patient with 48 bleeds and one patient with 96 bleeds).

^{**}No data available for the total number of spontaneous bleeds for one adolescent/adult.

^{††}No data available for the total number of spontaneous bleeds for two adolescents/adults.

^{‡‡}One outlier from the adult population in the prophylaxis group was removed (one patient with 96 bleeds).

^{§§}Data calculated based on all patients, considering zero traumatic bleeds in those patients who did not provide any data, except in eight patients who stated "data not known" and were not considered.

BR: annualized bleeding rate; AsBR: annualized spontaneous bleeding rate; AjBR: annualized joint bleeding rate; AtBR: annualized traumatic bleeding rate; IQR: interquartile range; SD: standard deviation.

Bleeds were mainly joint and muscular, with the knee (n = 160, 39.4%), ankle (n = 42, 10.3%) and elbow (n = 30, 7.4%) the most frequent bleeding locations. Although epistaxis was recorded as the second most frequent bleeding site (n = 50, 12.3%), it was mainly due to one patient who experienced a high number of nosebleeds (n = 48).

Hemostatic efficacy

A hemostatic efficacy rating of good or excellent was achieved for more than 95% of treated bleeding events, regardless of the type of bleeding and age (Table 4). The percentage of children who achieved an excellent hemostatic efficacy with the treatment of spontaneous bleeds was three times higher than that of adults, 62.5% vs. 20.9%, respectively (Table S3).

More than half of the patients, both pediatric and adolescents/adults, resolved bleeding episodes with one or two infusions (Table 4): 56.8% of children and 55.1% of adolescents/adults. The median number of infusions was similar for total bleeds (2.0, IQR 1.0-3.0), spontaneous

bleeds (2.0, IQR = 1.0-3.0), and traumatic bleeds (2.0, IQR = 1.0-4.0). Children needed more infusions than adolescents/adults to resolve spontaneous bleeding (median 4.0 [IQR = 1.5-8⁵] vs. 1.0 [IQR 1.0-3.0], respectively).

Bleeding episodes per patient and treatment

The median number of bleeding episodes per patient was 5.0 (IQR = 1.0-16.1) among patients with on-demand treatment (0.0 in children and 5.0 in adolescents/adults) and 2.0 (IQR = 1.0-4.0) among those with prophylactic treatment (2.0 in both children and adolescents/adults). The median number of spontaneous bleeding episodes was 2.0 (IQR = 0.0-11.0) in patients receiving on-demand treatment (0.0 in children and 3.5 in adolescents/adults) and 0.0 (IQR = 0.0-2.0) in those receiving prophylaxis (0.0 in both children and adolescents/adults); the median number of joint bleeding episodes was 2.0 (IQR = 0.0-11.0) in patients receiving on-demand treatment (0.0 in children and 3.5 in adolescents/adults) and 1.0 (IQR = 0.0-2.0) in those receiving prophylaxis (1.0 in both children and

Table 4. Hemostatic efficacy according to age and number of infusions needed to treat bleeds according to age

	Overall		Children		Adolescents/adults	
	n	%	n	% [†]	n	% [†]
Hemostatic efficacy*						
Excellent	100	29.20	16	43.2	84	27.5
Good	236	68.80	20	54.1	216	70.5
Moderate	7	2	1	2.7	6	2
Number of infusions						
0	5	0.97	-	-	5	1.6
1	165	32.10	16	43.2	149	47.8
1 or 2	193	37.55	21	56.8	172	55.1
3 or more	151	29.38	16	43.2	135	43.3

The hemostatic efficacy is shown as number and percentage of bleeds.

*Data not known for 58 bleeds out of the 406 total bleeds. Not applicable in five bleeds as there was no treatment for those bleeds.

[†]Percentage calculated over 37 bleeds in children and 312 bleeds in adults (data not known for 57).

Table 5. Distribution of the number of bleeding episodes per patient according to age, type of bleed, and treatment regimen

	Total		Adolescents/adults		Children*
	On demand	Prophylaxis	On demand	Prophylaxis	Prophylaxis
Total bleeding episodes	n = 16	n = 59	n = 15	n = 48	n = 11
Mean ± SD	8.4 ± 8.9	6.3 ± 15.1	8.9 ± 9.0	7.0 ± 16.6	3.4 ± 3.6
Median (IQR)	5.0 (1.0-16.0)	2.0 (1.0-4.0)	5.0 (1.0-20.0)	2.0 (1.0-4.0)	2.0 (1.0-6.0)
Min-max	0.0-24.0	0.0-96.0	0.0-24.0	0.0-96.0	0.0-12.0
Spontaneous bleeding episodes	n = 15	n = 56	n = 14 [†]	n = 45 [†]	n = 11
Mean ± SD	6.2 ± 7.5	4.0 ± 14.4	6.6 ± 7.6	4.8 ± 16.0	0.7 ± 1.1
Median (IQR)	2.0 (0.0-11.0)	0.0 (0.0-2.0)	3.5 (1.0-11.0)	0.0 (0.0-2.0)	0.0 (0.0-2.0)
Min-max	0.0-21.0	0.0-96.0	0.0-21.0	0.0-96.0	0.0-3.0
Joint bleeding episodes	n = 15	n = 57	n = 14 [‡]	n = 46 [‡]	n = 11
Mean ± SD	5.7 ± 6.7	3.5 ± 12.9	6.1 ± 6.8	4.0 ± 14.3	1.5 ± 2.3
Median (IQR)	2.0 (0.0-11.0)	1.0 (0.0-2.0)	3.5 (1.0-11.0)	1.0 (0.0-2.0)	1.0 (0.0-2.0)
Min-max	0.0-21.0	0.0-96.0	0.0-21.0	0.0-96.0	0.0-8.0
Traumatic bleeding episodes	n = 15	n = 52	n = 14 [§]	n = 14 [§]	n = 11
Mean ± SD	1.1 ± 1.5	1.3 ± 1.9	1.2 ± 1.5	1.0 ± 1.3	2.6 ± 3.2
Median (IQR)	0.0 (0.0-2.0)	0.5 (0.0-2.0)	0.5 (0.0-2.0)	0.0 (0.0-2.0)	2.0 (0.0-6.0)
Min-max	0.0-4.0	0.0-9.0	0.0-4.0	0.0-4.0	0.0-9.0

*Only one pediatric patient was treated on demand and had no bleeds reported.

[†]Missing data: four adolescents/adults (one on demand and three prophylaxis).

[‡]Missing data: three adolescents/adults (one on demand and two prophylaxis).

[§]Missing data: eight adolescents/adults (one on demand and seven prophylaxis).

IQR: interquartile range; SD: standard deviation.

adolescents/adults); and the median number of traumatic bleeding episodes was 0.0 (IQR = 0.0-2.0) in patients treated on-demand (0.0 in children and 0.5 in adolescents/adults) and 0.5 (IQR = 0.0-2.0) in patients treated prophylactically (2.0 in children and 0.0 in adolescents/adults) (Table 5).

Overall, the mean dose administered for bleeding treatment was 41.8 ± 13.0 IU/kg (45.0 ± 19.8 IU/kg for children and 41.4 ± 12.0 IU/kg for adolescents/adults).

According to the type of bleed, a higher mean dose was administered to patients with traumatic bleeds, 43.8 ± 19.0 IU/kg (Table 6).

The overall mean factor consumption to treat total bleeds was much higher in adolescents/adults compared to children, 7622.1 ± 15020.2 IU versus 3824.3 ± 7295.6 IU, respectively, as was the consumption to treat traumatic bleeds, 8313.7 ± 7161.7 IU vs. 2810.3 ± 6111.2 IU, respectively (Table 7). No

Table 6. Dose administered to treat bleeds according to type of bleed and age

Dose (IU/kg)	Total		Children		Adolescents/adults	
	n	Mean $\pm$ SD	n	Mean $\pm$ SD	n	Mean $\pm$ SD
Total bleeds* Overall	340	41.8 $\pm$ 13.0	35	45.0 $\pm$ 19.8	305	41.4 $\pm$ 12.0
Spontaneous bleeds† Overall	257	41.0 $\pm$ 10.3	6	44.2 $\pm$ 13.0	251	41.0 $\pm$ 10.2
Traumatic bleeds‡ Overall	80	43.8 $\pm$ 19.0	29	45.2 $\pm$ 21.1	51	43.0 $\pm$ 18.0

*Data not known for 61 bleeds out of the 406 total bleeds. Not applicable in five patients as there was no treatment for the bleeds.

†Data not known for 53 bleeds of the 312 spontaneous bleeds. Not applicable in two patients as there was no treatment for the spontaneous bleeds.

‡Data not known for two bleeds out of the 85 traumatic bleeds. Not applicable in three patients as there was no treatment for the traumatic bleeds.

IU: international units; SD: standard deviation.

Table 7. Total factor consumption needed to treat bleeds according to type of bleeds and age

Total factor consumption (IU)	Total		Children		Adolescents/adults	
	n	Mean $\pm$ SD	n	Mean $\pm$ SD	n	Mean $\pm$ SD
Total bleeds* Overall	344	7213.7 $\pm$ 14430.6	37	3824.3 $\pm$ 7295.6	307	7622.1 $\pm$ 15020.2
Spontaneous bleeds† Overall	261	7534.5 $\pm$ 16066.1	8	7500.0 $\pm$ 10229.5	253	7535.6 $\pm$ 16229.8
Traumatic bleeds‡ Overall	80	6318.8 $\pm$ 7265.4	29	2810.3 $\pm$ 6111.2	51	8313.7 $\pm$ 7161.7

*Data not known for 57 bleeds out of the 406 total bleeds. Not applicable in five patients as there was no treatment for the bleeds.

†Data not known for 49 bleeds of the 312 spontaneous bleeds (prophylaxis). Not applicable in two patients as there was no treatment for the spontaneous bleeds.

‡Data not known for two bleeds out of the 85 traumatic bleeds. Not applicable in three patients as there was no treatment for the traumatic bleeds.

SD: standard deviation.

differences were found between both age groups in factor consumption for the treatment of spontaneous bleeds.

Joint health status

In general, patients presented moderate/good joint condition, with a maximum score of 17 points out of 66 on the HJHS scale. Overall, 21 of the 45 patients evaluated (46.7%) had perfect joint health status (score 0), including three patients (27.3%) with on-demand treatment and 18 with prophylactic treatment (52.9%). By age group, children showed the best status; 71.4% had no impairment in any of the joints assessed, except one child who presented swelling and $< 15^\circ$ in left ankle flexion contracture, and one child who presented $< 15^\circ$ in left knee flexion contracture. All children (n = 7) scored ≤ 2 on the HJHS scale (the only child treated on demand and four of the six children treated prophylactically scored 0). Almost half of adolescents/

adults (n = 16, 42.1%) had no impairment according to the HJHS scale. In patients with some type of impairment (n = 22), the total sum ranged from 1 to 17 points (20% of patients with on-demand treatment and 64.3% of patients treated on prophylaxis scored ≤ 2) (Table S4).

QoL

PHYSICAL ACTIVITY

Data on physical activity levels were available for 59 patients (78.7%), 13 patients with on-demand treatment and 46 patients on prophylaxis (10 children and 49 adolescents/adults). The patient's own perception and the physician's perception were concordant. All children were perceived as moderately or vigorously active, in terms of physical exercise. Among the adolescent/adult population, 85.7% of patients, according to the patient's own perception, and 83.7%, according to the physician's perception, were considered "active"

(moderately, vigorously, or extremely active), while the corresponding percentages of patients who were considered “sedentary or extremely inactive” were 14.3% and 16.3%, respectively. In general, adult patients on prophylaxis were perceived as more active than those with on-demand treatment.

Patient's ability to walk

Regarding the ability to walk, more adult patients, compared to children, did not need any help, 81.4% versus 75.0%. Among those who needed assistance, 12.7% of adolescents/adults required a walker, cane, crutches, or wheelchair, while 8.3% of children needed crutches (information not known for 16.7% of patients).

Chronic joint pain

Overall, patients treated on prophylaxis had less chronic joint pain than those with on-demand treatment, 18.6% vs. 56.3%, respectively. Among patients on prophylactic treatment (information not known for 20.3% of patients), more children had no chronic joint pain compared to adolescents/adults, 72.7% vs. 58.3%, respectively.

Questionnaire EQ-5D-5L and VAS

In addition to physical activity, the EQ-5D-5L questionnaire and the VAS were used to assess patient QoL. The EQ-5D-5L questionnaire showed that one-third of all patients (21 of 63, 33.3%) considered themselves to be in their best possible state of health (full health, i.e., level 1 in all five dimensions). According to the type of treatment, patients on a prophylactic regimen had better QoL and fewer problems than patients treated on demand: 39.6% vs. 13.3% of patients, respectively, did not report problems in any dimension (Table 8).

The VAS scale ranges from 0 to 100, where 100 is the best imaginable state of health. According to this scale, patients treated prophylactically reported a better self-rated health status than patients treated on demand, with mean VAS scores of 82.5 ± 15.6 vs. 62.7 ± 20.0 , respectively (Table 8).

Safety

Overall, five patients (6.7%) presented adverse events, not related to the medication, over the last 24 months (two children [16.7%] and three adolescents/adults [4.8%]), of which two of them (all adolescents/adults)

Table 8. Self-rated health status using the EQ-5D 5L questionnaire and VAS. Proportion of “no problem” responses

EQ-5D 5L		
Dimension - N (%)	On demand (n = 15)	Prophylaxis (n = 48)
Mobility No problems in walking about	5 (33.3)	25 (52.1)
Self-care No problems washing or dressing myself	11 (73.3)	42 (87.5)
Usual activities No problems doing my usual activities	9 (60.0)	35 (72.9)
Pain/discomfort No pain or discomfort	4 (26.7)	23 (47.9)
Anxiety/depression Not anxious or depressed	10 (66.7)	38 (79.2)
Full health (11111) - N (%)	2 (13.3%)	19 (39.6%)
VAS		
N	15	48
Mean $\pm$ SD	62.7 ± 20.0	82.5 ± 15.6
Median (IQR)	60.0 (50.0-75.0)	87.5 (75.0-95.0)

IQR: interquartile range; SD: standard deviation; VAS: visual analogue scale.

were serious (head trauma in an adult patient treated on demand and right femur fracture in an adult patient with prophylactic treatment). They resolved without consequences in all cases except for one, which was resolved with sequelae (right femur fracture). No adverse reactions related to concentrates were observed.

Prophylactic treatment with EHL rIX-FP (albutrepenonacog alfa)

A total of six patients, a median age of 24.5 years old (ranging from 12 to 62 years old) from the study were treated prophylactically with rIX-FP (albutrepenonacog alfa) over the complete study period. A specific data extraction and analysis of this subgroup revealed a median ABR of 0.5 (IQR = 0.0-1.0), median AsBR of 0.2 (IQR = 0.0-1.0), and median AjBR of 0.2 (IQR = 0.0-1.0). Eleven bleeds were reported on four patients (five spontaneous, four traumatic, and five joint bleeds). Five out eleven bleeds did not require additional factor administration to control the bleed. Excellent or good hemostatic efficacy was achieved in every treated bleed.

Two of these patients were treated with albutrepenonacog alfa once every 15 days, with a mean factor consumption of 9,750 IU/month; one patient was given albutrepenonacog alfa every 14 days (mean factor consumption = 8,000 IU/month); and one received it every 10 days (mean factor consumption = 10,500 IU/month). One patient switched to albutrepenonacog alfa twice weekly (mean factor consumption = 12,000 IU/month) following severe ankle synovitis, which resolved after this switch. The remaining patient was treated every 21 days, and after a traumatic bleeding event switched to a 14-day regimen with a mean factor consumption of 10,000 IU/month.

Furthermore, these patients reported a mean QoL score of 92 according to the VAS. According to the EQ-5D-5L questionnaire, 66.7% of these patients (n = 4) scored 1 in all dimensions. Finally, none of the six patients treated with albutrepenonacog alfa developed FIX inhibitors or reported adverse reactions.

Discussion

This cross-sectional study performed with 75 patients (12 children [≤ 12 years] and 63 adolescents/adults) sheds some light on the current management of hemophilia B in clinical practice in Spain and Portugal. In addition, it relates the therapeutic strategies applied to the resulting QoL of these patients.

In this study, the majority of patients (78.7%) were treated with a prophylactic regimen. Prophylaxis in severe hemophilia B patients is the evidence-based standard of care, as it improves health outcomes as compared with on-demand regimens¹⁰. Of these outcomes, we found the median ABR and AsBR to be lower in patients receiving prophylactic treatment (ABR = 1.0; IQR = 0.5-2.0; AsBR = 0.0; IQR = 0.0-0.5) than in those treated on demand (ABR = 2.5; IQR = 0.5-8.0; AsBR = 1.0; IQR = 0.0-5.5). Likewise, the number of bleeding episodes per patient was higher for patients treated on demand. This is consistent with previous evidence and confirms the prevention and reduction of bleeds as the main advantage of prophylaxis vs. on-demand treatment¹⁷. The decrease in bleeding episodes may certainly correlate with better joint health status, which translates into less chronic joint pain, among other effects. Although prophylaxis has been used less frequently in hemophilia B than in hemophilia A, it is recommended in treatment guidelines as there is sufficient evidence of the health benefits of this regimen¹⁸. Therefore, the establishment of prophylactic therapy that reduces bleeding episodes directly impacts the prevention of arthropathy¹⁹. This is also reflected in

our study, where patients on prophylaxis had less chronic joint pain than those with on-demand treatment, 18.6% vs. 56.3%, respectively. Moreover, among these, more children had no chronic joint pain compared to adolescents/adults, 72.7% vs. 58.3%, respectively. This additional difference in joint health between children and adults further supports the recommendation for early prophylaxis as the standard of care, as endorsed by the World Federation of Hemophilia, the World Health Organization, and many other hemophilia organizations worldwide. According to these guidelines, an early prophylaxis approach provides the best long-term outcomes²⁰. Moreover, adult patients on prophylaxis from this sample were perceived as more active than those with on-demand treatment when evaluating the physical activity from both the patient's and the physician's perspective. The aforementioned findings, such as fewer bleeds and better physical activity and joint health status, reinforce the known influence of prophylactic treatment on patient QoL. Furthermore, patients on a prophylactic regimen from our study reported significantly better QoL and fewer problems than those treated on demand according to the EQ5D5L questionnaire and VAS. The evaluation of joint health in this study has been limited to the Hemophilia Joint Health Score (HJHS) defined by the World Federation of Hemophilia guidelines as the best-studied score for physical examination of hemophilic patients²⁰. The lack of an ultrasound scoring system of joint health, like HEAD-US, together with the HJHS is a clear limitation of the study. The use of ultrasound (US) scoring systems to assess early hemophilic arthropathy is recommended by the World Federation of Hemophilia guidelines²⁰. HEAD-US is a validated simplified scanning procedure and scoring method for early arthropathy detection with ultrasound²¹ that has been used previously to evaluate joint health on hemophilia B in Spain, showing its potential to guide and individualize hemophilia B treatment based on joint health at the early stage of arthropathy development²².

Despite the known association of prophylaxis with better long-term outcomes in hemophilia B patients, and the wide range of FIX replacement products available, there is still room for improvement in the therapeutic management of hemophilia B. It has been widely recognized that the use of EHL factor replacement products can change the landscape of hemophilia treatment. This is particularly important for hemophilia B, as these products allow significantly higher trough levels of FIX to be achieved, reducing the frequency of intravenous injections as compared with SHL products²⁰. Studies

show that this translates into higher patient adherence and lower bleeding rates, although evidence is still limited²³. In this analysis, six patients from Spanish centers were on prophylactic treatment with an EHL-rFIX product, albutrepenonacog alfa. In Spain, these 6 patients came from albutrepenonacog alfa clinical trial and extended the treatment over the 24 months study period. Remarkably, they received the treatment for 2 years with intervals up to 15 days, achieving excellent effectiveness (median ABR = 0.50 [IQR = 0-2.5]; median AsBR = 0.2 [IQR = 0.0-1.0]) and reporting a mean QoL score of 92 according to the VAS. Moreover, one patient switched to albutrepenonacog alfa following severe ankle synovitis, which resolved after this switch. In addition to better efficacy outcomes, previous studies have reported generally lower consumption of IU with EHL-FIX products as compared to SHL replacement factors²⁴. In line with this evidence, in our study, the median patient consumption per week (IU/kg) over the last prophylactic dose regimen with albutrepenonacog alfa was significantly lower than with standard half-life products (almost half). Thus, these data support the suggestion that therapeutic management of hemophilia B patients could be further enhanced, although more studies with larger sample sizes are necessary to compare the benefits of EHL-FIX products with the standard therapies.

Finally, one of the limitations of this study is that epidemiological, clinical, and treatment outcome data were retrospectively collected from patient medical records and hence they are restricted to the available information. On the other hand, even though the sample size might seem small, it is not scant when we consider its proportion to the total hemophilia B population of Spain and Portugal. Nevertheless, further prospective analysis with a higher number of patients should be performed.

Conclusions

In summary, this study gives us some insight into the management of hemophilia B patients in Spain and Portugal, including the treatment strategies used and their impact on the patient's clinical outcomes and QoL. Our findings are in line with previous evidence and confirm the benefits of prophylactic regimens over on-demand treatments. In fact, they show an association of prophylaxis with a reduction in annualized bleeding rates, better joint health, and improved QoL. The results also highlight the additional advantages of EHL-FIX products, such as the lower consumption of factor units, decreased annualized bleeding rates, extended treatment intervals, and improved patient-reported QoL, as compared with the entire

prophylactic group, which could impact hemophilia B treatment management and patients' disease burden.

Supplementary data

Supplementary data are available at DOI: 10.24875/SANGREE.22000010. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

Author contribution

All authors made substantial contributions to the acquisition of the data for the work. All authors critically revised the manuscript for important intellectual content, approved the final version submitted, and agreed to be accountable for all aspects of the work. R. S. and V. J. Y. as study coordinators and M. T. A. R. as first author participated actively in paper writing and first draft reviews.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text.

The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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