

Delphi consensus on managing prophylactic treatment in patients with severe hemophilia A in Spain

Estudio Delphi del manejo del tratamiento profiláctico en pacientes con hemofilia A grave en España

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Abstract

Objective: To evaluate, using the Delphi method, the management of prophylactic treatment, bleeding control and surgery with standard-life (SHL) factor VIII (FVIII), extended-half-life (EHL). FVIII and emicizumab in patients with severe hemophilia A (HA) in Spain. **Methods:** A 1st questionnaire was validated by a Scientific Committee and sent to 85 hematologists. "Consensus" or "intermediate consensus" was determined when $\geq 80\%$ or $\geq 70\%$ of the experts selected the same answer. A 1st questionnaire was sent to the experts of the 1st round, and a discussion process with the scientific committee was started. **Results:** In both the 1st and 2nd rounds 27 and 24 experts participated, respectively. "Consensus" was reached on 107 items, "intermediate consensus" on 15, and "no consensus" on 14. In prophylactic treatment, 93% of the experts use recombinant FVIII. A guideline of 20-50 and 20-40 IU/kg 3 times/week was agreed for pediatric and adults treated with SHL recombinant FVIII, respectively and 25-65 IU/kg every 3-5 days for patients on EHL FVIII. Moderate/severe bleeding is treated similarly and intensively with administrations every 12 h. There is consensus on management regimens regarding major surgery. In emicizumab prophylaxis, consensus was not reached regarding monitoring. **Conclusions:** There is a great consensus in the management of patients with HA in Spain.

Keywords: Delphi method. Hemophilia A. Spain. Prophylactic treatment. Bleeding control. Surgery.

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Resumen

Objetivo: Evaluar, mediante el método Delphi, el tratamiento profiláctico, el control de sangrados y cirugía con FVIII de vida estándar (SHL), FVIII de vida media extendida (EHL) y emicizumab en pacientes con hemofilia A (HA) grave en España.

Métodos: Un Comité Científico validó un 1^{er} cuestionario y se envió a 85 hematólogos. Se determinó “consenso” o “consenso intermedio” cuando $\geq 80\%$ o $\geq 70\%$ de los expertos seleccionaron la misma respuesta. Se envió un segundo cuestionario y se llevó a cabo un proceso de deliberación con el Comité Científico. **Resultados:** En la 1^a y 2^a ronda participaron 27 y 24 expertos, respectivamente. Se alcanzó “consenso” en 107, “consenso intermedio” en 15 y “no consenso” en 14 de las preguntas. En profilaxis, el 93% utilizan el FVIII recombinante. Se acordó 20-50 y 20-40 UI/kg, 3 veces/semana para pediátricos y adultos con SHL rFVIII, respectivamente; y 25-65 UI/kg cada 3-5 días para pacientes con FVIII EHL. Las hemorragias moderadas/graves se tratan de forma intensiva con administraciones cada 12 h. Existe consenso sobre las pautas de administración para cirugía mayor. En profilaxis con emicizumab, no se alcanzó consenso sobre la monitorización. **Conclusiones:** Existe un gran consenso en el manejo de los pacientes con HA en España.

Palabras clave: Método Delphi. Hemofilia A. España. Profilaxis. Control de sangrados. Cirugía.

Introduction

Hemophilia A (HA) is an inherited bleeding disorder caused by factor VIII (FVIII) deficiency. HA is responsible for 80% to 85% of the hemophilia cases and has an incidence rate of 1/5000 birth^{1,2}.

HA is mainly characterized by joint (hemarthrosis) and muscle hemorrhages^{1,3}. Bleeding episodes are related to plasma levels of the deficient factor and are more frequent and significant in patients with severe forms of the disease ($< 1\%$ of the blood coagulation activity of FVIII). In severe forms (32.8% of the patients with HA in Spain⁴), spontaneous and recurrent bleeding cause hemophilic arthropathy^{5,6}, which greatly affects the patients' health-related quality of life^{7,8}. In addition, some serious bleeding episodes, such as bleeding into the gastrointestinal tract or central nervous system can even become life threatening⁹⁻¹¹.

The objectives for managing patients with HA are early prevention and treatment of bleeding episodes to avoid joint damage^{1,3}. Management is based on supplying the deficient clotting factor through replacement therapy through intravenous injection of FVIII concentrates at an appropriate dose. This depends on the patient age, disease severity, and location and severity of the bleeding episode^{1,3}. Plasma-derived and recombinant standard half-life (SHL) recombinant FVIII (rFVIII) replacement therapy has been, for a long time, the main method for the prevention and treatment of bleeding episodes. Recently, extended half-life (EHL) recombinant FVIII (rFVIII) products were introduced to increase protection and improve the health-related quality of life of HA patients by providing higher plasma levels through slower clearance¹².

FVIII concentrates can be administered on-demand after a bleeding episode occurs to control and stop the

bleeding or periodically, to prevent spontaneous bleeding, thus maintaining enough FVIII activity plasma (prophylactic treatment)^{1,3,13}.

Currently, the advised treatment for pediatric and adult populations with severe HA is prophylactic factor replacement therapy^{1,14-16}. Compared to on-demand treatment, this treatment regimen has been shown to significantly reduce the number of bleeding episodes¹⁷⁻¹⁹, thus leading to a decrease in the development of arthropathy, reduced hospital admissions, less work absenteeism, and improved health-related quality of life for the patients¹⁹. However, as some patients may experience hemorrhages, instead of prophylactic treatment, an individualized approach considering not only FVIII plasma levels but also other elements, such as bleeding phenotype, lifestyle, joint condition, physical activity level, and compliance to treatment, is highly advised²⁰.

Over the last few years, new treatments have become available for patients with HA; these treatments include EHL rFVIII concentrates and non-replacement therapy (such as emicizumab).

Facing the absence of real-world data on the management of patients who might be receiving these new treatments in Spain, the objective of this study is to evaluate the implementation of these treatments and their management in real life using the Delphi method to address all scenarios: prophylaxis regimen, management of bleeding episodes and surgical approaches.

Materials and methods

Study design

A qualitative study was developed using the modified Delphi method, a non-face-to-face decision-making

technique that relies on the anonymous opinions of a panel of experts who respond multiple rounds of an online questionnaire. Answering the questionnaire in multiple rounds allows the experts to reconsider and adjust their positions, thereby facilitating a consensus response to the topic of interest²¹⁻²³.

The study was conducted in four phases: (a) establishment of the scientific committee responsible for the selection and validation of the items included in the questionnaire; (b) selection of a panel of hematologists specialized in HA; (c) dissemination of an online questionnaire in two rounds, with intermediate processing and sharing of the results with experts; and (d) compilation and analysis of the final results. A final meeting was conducted to discuss the conclusions with the scientific committee.

Selection of the panel of experts and scientific committee

A scientific committee of 5 hematologists with extensive experience in managing pediatric and adult hemophilia was created. This scientific committee was responsible for selecting and validating the items that would be included in the questionnaires and for reviewing and agreeing on the results obtained using the Delphi method. Subsequently, a panel of experts specialized in HA was selected. Eighty-five national hematologists were invited to participate. Of those 85 experts, 27 participated in the first round, and 24 continued to the second round of the project. Regarding the geographic distribution of the participating experts, 12 autonomous communities were represented: Andalusia (Complejo Hospitalario de Jaén, Hospital Regional Universitario de Málaga, Hospital Universitario Puerta del Mar, Hospital Virgen de las Nieves), Aragon (Hospital Universitario Miguel Servet), Asturias (Hospital Universitario Central de Asturias), the Canary Islands (C.H.U. Insular-Materno Infantil de Canarias), Cantabria (Hospital Universitario Marqués de Valdecilla), Castilla-La Mancha (Complejo Hospitalario de Toledo, Hospital Universitario de Guadalajara), Castile and León (Complejo Asistencial de Ávila, Hospital Universitario de Burgos, Hospital Universitario de Salamanca), Catalonia (Hospital de la Santa Creu i Sant Pau, Hospital Sant Joan de Déu, Hospital Vall d'Hebrón), the Community of Madrid (Hospital Universitario La Paz), the Valencian Community (Hospital General Universitario de Alicante, Hospital Universitario y Politécnico La Fe), Galicia (Hospital Álvaro Cunqueiro), and the Basque Country (Hospital Universitario Araba, Hospital Universitario

Cruces). A total of 22 Spanish hospitals participated in the study. Two of them are reference centers for congenital bleeding disorders.

Development of the questionnaire

A comprehensive review of the available literature was conducted with from two external consultants. Also, an algorithm was designed for patients with severe HA without inhibitors under prophylactic treatment (Fig. 1). The treatment algorithm and the items that should be included in the first-round questionnaire were reviewed and validated with the members of the scientific committee.

A first draft of the questionnaire was prepared and reviewed by the scientific committee. The proposals made by the committee were reviewed by external consultants and synthesized to unanimously achieve a satisfactory combined version.

Finally, the first-round questionnaire included 136 items related to prophylactic treatment, bleeding management, and surgical approaches for patients with severe HA. All these items were mandatory to be assessed by each of the panelists. The questions included in the questionnaire were grouped into the following categories: pediatric patients treated with SHL FVIII, pediatric patients treated with EHL rFVIII, adult patients treated with SHL FVIII, adult patients treated with EHL rFVIII, and patients treated with emicizumab.

Each question had several predetermined options to choose from and an open answer alternative. A single answer per question was allowed. All questions were mandatory to be answered to gather the opinion of all panelists.

The first-round online questionnaire was available from June through October 2019. After the results from the first round were analyzed, a second-round online questionnaire, available from November 2019 through January 2020, was sent only to the 27 experts who participated in the first round. The second round only included those questions where consensus was not reached in the first round.

The overall process surveillance and data analysis were conducted by the scientific committee with help from 2 external consultants.

Data analysis

Both the fieldwork and data collection were conducted in two rounds, during which experts were contacted.

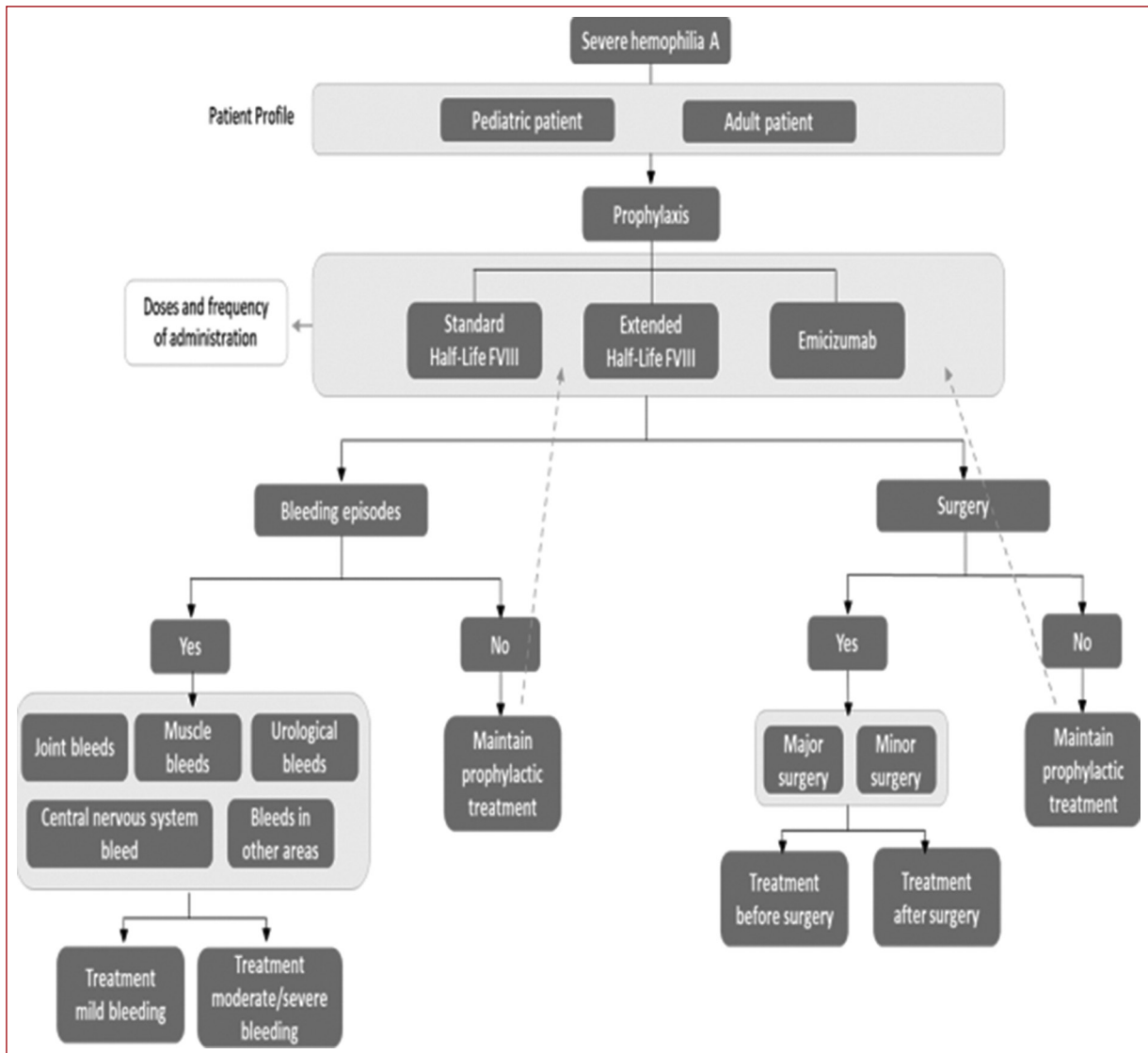


Figure 1. Prophylactic treatment algorithm in patients with severe hemophilia A.

Two reminders were sent in each round to increase the response rate. The consensus rounds were conducted through an online questionnaire designed in Google Forms to facilitate completion.

After the first round, the consensus rate for each item was evaluated. A “consensus” was established when > 80% of the experts selected the same answer, a “moderate consensus” when > 70% of the panelists agreed on the same response, and “no consensus” when < 70% of the panelists agreed on the same response. Questions without consensus were reanalyzed in coordination with the scientific committee by eliminating answers where the answer was $n = 1$ or by grouping answers to assess whether any item had reached consensus or not.

In the second round, the panelists reassessed their responses by considering the overall results obtained in the first round.

The results were analyzed based on the aforementioned criteria, and the final results were obtained. A final meeting was held with the scientific committee to review consensus, and discuss the clinical meaning of the conclusions reached.

Fig. 2 shows the different phases of the Delphi method.

Results

Following the first round, the expert panel reached a consensus on 73 (54%) of the 136 evaluated items.

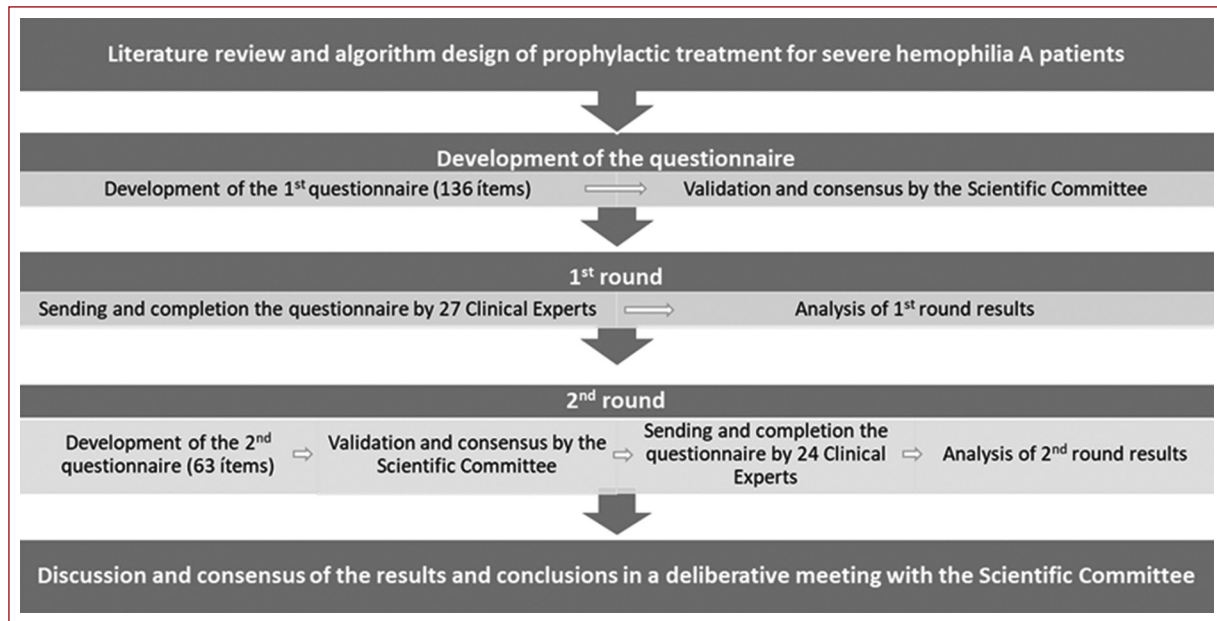


Figure 2. Delphi method process and algorithm design.

Table 1. Results on prophylactic treatment in patients with severe hemophilia A

	Response	Agreement	Result	Comments
Prophylactic treatment				
What type of SHL FVIII would you give, plasmatic or recombinant?				
Pediatric patients on FVIII (n = 27)	Recombinant SHL FVIII	92.6%	Consensus 1 st round	-
Adult patients on FVIII (n = 27)	Recombinant SHL FVIII	92.6%	Consensus 1 st round	-
What administration regimen would the patient receive?				
Pediatric patients on SHL rFVIII (n = 24)	20-50 IU/kg, 3 times weekly	91.7%	Consensus 1 st round	Responses were grouped to achieve consensus
Pediatric patients on EHL rFVIII (n = 24)	25-65 IU/kg every 3-5 days	70.8%	Moderate consensus 2 nd round	-
Adult patients on SHL rFVIII (n = 24)	20-40 IU/kg, 3 times weekly	87.5%	Consensus 1 st round	-
Adult patients on EHL rFVIII (n = 27)	25-65 IU/kg every 3-5 days	81.5%	Consensus 1 st round	-

FVIII: factor VIII; SHL rFVIII: standard half-life recombinant FVIII; EHL rFVIII: extended half-life recombinant FVIII.

No consensus was reached on 63 items (46%). In the second round, consensus was reached on 49 (78%) of the 63 remaining items (34 items achieved a consensus and 15 moderate consensus). Overall, consensus was reached on 107 items (79%), moderate consensus was on 15 items (11%), and no consensus on 14 questions (10%).

The results of the Delphi method after the two rounds are shown on [tables 1-4](#).

Prophylactic treatment

Ninety-three percent of the consulted experts used recombinant SHL FVIII for prophylaxis in pediatric (aged < 12 years) and adult patients (aged ≥ 12 years) with severe HA ([Table 1](#)). Regarding the administration regimen, for pediatric and adult patients treated with SHL rFVIII, doses of 20-50 international units (IU)/kg 3 times per week and 20-40 IU/kg 3 times per week, respectively, were agreed on. In patients treated with EHL

Table 2. Results on the control of bleeding episodes in patients with severe hemophilia A

	Response	Agreement	Result	Comments
Moderate/severe bleeding				
With moderate/severe bleeding, would you administer a continuous or bolus injection?				
Pediatric patients on SHL rFVIII (n = 24)	Bolus injection	70.8%	Moderate consensus 2 nd round	-
Pediatric patients on EHL rFVIII (n = 27)	Bolus injection	100.0%	Consensus 1 st round	-
Adult patients on SHL rFVIII (n = 27)	Bolus injection	92.6%	Consensus 1 st round	-
Adult patients on EHL rFVIII (n = 27)	Bolus injection	100.0%	Consensus 1 st round	-
Mild joint bleeding				
What administration regimen would the patient receive?				
Pediatric patients on SHL rFVIII (n = 25)	20-50 IU/kg, single dose	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Pediatric patients on EHL rFVIII (n = 25)	20-50 IU/kg, single dose	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Adult patients on SHL rFVIII (n = 24)	No consensus			
Adult patients on EHL rFVIII (n = 27)	20-50 IU/kg, single dose	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Moderate/severe joint bleeding				
If circumstances allow, would you consider performing evacuating arthrocentesis?				
Pediatric patients on SHL rFVIII (n = 24)	Yes	95.8%	Consensus 2 nd round	-
Pediatric patients on EHL rFVIII (n = 24)	Yes	95.8%	Consensus 2 nd round	-
Adult patients on SHL rFVIII (n = 24)	Yes	95.8%	Consensus 2 nd round	-
Adult patients on EHL rFVIII (n = 24)	Yes	95.8%	Consensus 2 nd round	-
Would you administer a loading dose of 40-50 IU/kg?				
Pediatric patients on SHL rFVIII (n = 27)	Yes	81.5%	Consensus 1 st round	-
Pediatric patients on EHL rFVIII (n = 27)	Yes	85.2%	Consensus 1 st round	-
Adult patients on SHL rFVIII (n = 27)	Yes	88.9%	Consensus 1 st round	-
Adult patients on EHL rFVIII (n = 27)	Yes	88.9%	Consensus 1 st round	-
What administration regimen would the patient receive from day 1 to day 2?				
Pediatric patients on SHL rFVIII (n = 27)	20-50 IU/kg, every 8-12 h	85.2%	Consensus 1 st round	Responses were grouped to achieve consensus
Pediatric patients on EHL rFVIII (n = 26)	20-50 IU/kg, every 12-24 h	88.5%	Consensus 1 st round	Responses were grouped to achieve consensus
Adult patients on SHL rFVIII (n = 24)	20-35 IU/kg every 8-12 h	87.5%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Adult patients on EHL rFVIII (n = 25)	20-35 IU/kg every 12-24 h	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
What administration regimen would the patient receive from day 3?				
Pediatric patients on SHL rFVIII (n = 24)	20-50 IU/kg every 24 h, 3-5 days	100.0%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Pediatric patients on EHL rFVIII (n = 24)	20-50 IU/kg every 24 h, 3-5 days	91.7%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Adult patients on SHL rFVIII (n = 24)	20-35 IU/kg every 12-24 h, 5 days	87.5%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round

(Continues)

Table 2. Results on the control of bleeding episodes in patients with severe hemophilia A (*continued*)

	Response	Agreement	Result	Comments
Adult patients on EHL rFVIII (n = 23)	20-35 IU/kg every 24 h, 3-5 days	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Mild muscle bleeding				
What administration regimen would the patient receive?				
Pediatric patients on SHL rFVIII (n = 26)	20-40 IU/kg, 1-3 days	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Pediatric patients on EHL rFVIII (n = 27)	20-40 IU/kg, 1-3 days	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Adult patients on SHL rFVIII (n = 26)	20-40 IU/kg, 1-3 days	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Adult patients on EHL rFVIII (n = 26)	20-40 IU/kg, 1-3 days	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Moderate/severe muscle bleeding				
Would you administer a loading dose of 40-50 IU/kg?				
Pediatric patients on SHL rFVIII (n = 27)	Yes	85.2%	Consensus 1 st round	-
Pediatric patients on EHL rFVIII (n = 27)	Yes	85.2%	Consensus 1 st round	-
Adult patients on SHL rFVIII (n = 27)	Yes	92.6%	Consensus 1 st round	-
Adult patients on EHL rFVIII (n = 27)	Yes	100.0%	Consensus 1 st round	-
What administration regimen would the patient receive from day 1 to day 3?				
Pediatric patients on SHL rFVIII (n = 27)	20-50 IU/kg every 8-12 h	92.6%	Consensus 1 st round	Responses were grouped to achieve consensus
Pediatric patients on EHL rFVIII (n = 26)	20-50 IU/kg every 12-24 h	88.5%	Consensus 1 st round	Responses were grouped to achieve consensus
Adult patients on SHL rFVIII (n = 25)	20-35 IU/kg every 8-12 h	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Adult patients on EHL rFVIII (n = 26)	20-35 IU/kg every 12-24 h	84.6%	Consensus 1 st round	Responses were grouped to achieve consensus
What administration regimen would the patient receive from day 4?				
Pediatric patients on SHL rFVIII (n = 24)	20-50 IU/kg every 12-24 h, 7-10 days	83.3%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Pediatric patients on EHL rFVIII (n = 24)	20-50 IU/kg every 12-24 h, 7-10 days	87.5%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Adult patients on SHL rFVIII (n = 24)	20-35 IU/kg every 12-24 h, 7-10 days	95.8%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Adult patients on EHL rFVIII (n = 24)	20-35 IU/kg every 12-24 h, 7-10 days	91.6%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Mild urological bleeding				
Would you treat the patient with FVIII?				
Pediatric patients on SHL rFVIII (n = 24)	No	75.0%	Moderate consensus 2 nd round	-
Pediatric patients on EHL rFVIII (n = 24)	No	83.3%	Consensus 2 nd round	-
Adult patients on SHL rFVIII (n = 24)	No	79.2%	Moderate consensus 2 nd round	-
Adult patients on EHL rFVIII (n = 24)	No	79.2%	Moderate consensus 2 nd round	-

(Continues)

Table 2. Results on the control of bleeding episodes in patients with severe hemophilia A (*continued*)

	Response	Agreement	Result	Comments
Would the patient receive a corticosteroid regimen?				
Pediatric patients on SHL rFVIII (n = 23)	No	73.9%	Moderate consensus 2 nd round	-
Pediatric patients on EHL rFVIII (n = 23)	No	73.9%	Moderate consensus 2 nd round	-
Adult patients on SHL rFVIII (n = 23)	No	73.9%	Moderate consensus 2 nd round	-
Adult patients on EHL rFVIII (n = 23)	No	73.9%	Moderate consensus 2 nd round	-
Moderate/severe urological bleeding				
What administration regimen would the patient receive?				
Pediatric patients on SHL rFVIII (n = 24)	No consensus			
Pediatric patients on EHL rFVIII (n = 24)	15-40 IU/kg every 24 h, 3-5 days	83.3%	Consensus 2 nd round	Responses were grouped to achieve consensus
Adult patients on SHL rFVIII (n = 23)	No consensus			
Adult patients on EHL rFVIII (n = 23)	No consensus			
Moderate/severe central nervous system bleeding				
Would you administer a loading dose of 50-70 IU/kg?				
Pediatric patients on SHL rFVIII (n = 27)	Yes	100.0%	Consensus 1 st round	-
Pediatric patients on EHL rFVIII (n = 27)	Yes	100.0%	Consensus 1 st round	-
Adult patients on SHL rFVIII (n = 27)	Yes	100.0%	Consensus 1 st round	-
Adult patients on EHL rFVIII (n = 27)	40-70 IU/kg	100.0%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
What administration regimen would the patient receive from day 1 to day 7?				
Pediatric patients on SHL rFVIII (n = 24)	20-50 IU/kg every 8-12 h	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Pediatric patients on EHL rFVIII (n = 24)	20-50 IU/kg every 8-12 h	83.3%	Consensus 1 st round	Responses were grouped to achieve consensus
Adult patients on SHL rFVIII (n = 25)	20-35 IU/kg every 8-12 h	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Adult patients on EHL rFVIII (n = 24)	20-35 IU/kg every 8-12 h	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
What administration regimen would the patient receive from day 7?				
Pediatric patients on SHL rFVIII (n = 24)	20-50 IU/kg every 12-24 h, 14 days	87.5%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Pediatric patients on EHL rFVIII (n = 24)	20-50 IU/kg every 12-24 h, 14 days	91.6%	Consensus 2 nd round	Responses were grouped to be re-asked in the second round
Adult patients on SHL rFVIII (n = 24)	20-35 IU/kg every 12-24 h, 14 days	91.6%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Adult patients on EHL rFVIII (n = 24)	20-35 IU/kg every 12-24 h, 14 days	83.3%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round

(Continues)

Table 2. Results on the control of bleeding episodes in patients with severe hemophilia A (*continued*)

	Response	Agreement	Result	Comments
Mild bleeding in other areas				
What administration regimen would the patient receive?				
Pediatric patients on SHL rFVIII (n = 27)	20-40 IU/kg, single dose	96.3%	Consensus 1 st round	-
Pediatric patients on EHL rFVIII (n = 27)	20-40 IU/kg, single dose	96.3%	Consensus 1 st round	-
Adult patients on SHL rFVIII (n = 27)	20-40 IU/kg, single dose	96.3%	Consensus 1 st round	-
Adult patients on EHL rFVIII (n = 27)	20-40 IU/kg, single dose	96.3%	Consensus 1 st round	-
Moderate/severe bleeding in other areas				
Would you administer a loading dose of 40-50 IU/kg?				
Pediatric patients on SHL rFVIII (n = 27)	Yes	88.9%	Consensus 1 st round	-
Pediatric patients on EHL rFVIII (n = 27)	Yes	88.9%	Consensus 1 st round	-
Adult patients on SHL rFVIII (n = 27)	Yes	92.6%	Consensus 1 st round	-
Adult patients on EHL rFVIII (n = 27)	Yes	96.3%	Consensus 1 st round	-
What administration regimen would the patient receive from day 1 to day 3?				
Pediatric patients on SHL rFVIII (n = 26)	20-50 IU/kg, every 8-12 h	80.8%	Consensus 1 st round	Responses were grouped to achieve consensus
Pediatric patients on EHL rFVIII (n = 25)	20-50 IU/kg, every 12-24 h	88.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Adult patients on SHL rFVIII (n = 25)	20-50 IU/kg, every 8-12 h	88.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Adult patients on EHL rFVIII (n = 26)	20-35 IU/kg, every 12-24 h	84.6%	Consensus 1 st round	Responses were grouped to achieve consensus
What administration regimen would the patient receive from day 4?				
Pediatric patient SHL rFVIII (n = 24)	20-50 IU/kg every 12-24 h, 7-10 days	83.3%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Pediatric patient EHL rFVIII (n = 24)	No consensus			
Adult patient SHL rFVIII (n = 24)	20-50 IU/kg every 12-24 h, 7-10 days	87.5%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Adult patient EHL rFVIII (n = 24)	20-35 IU/kg every 24 h, 7-10 days	91.7%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round

SHL rFVIII: standard half-life recombinant FVIII; EHL rFVIII: extended half-life recombinant FVIII.

rFVIII, a regimen of 25-65 IU/kg every 3-5 days was established for both pediatric and adult patients (Table 1).

Bleeding episodes

The results of the questions regarding treatment of bleeding episodes are shown on Table 2.

Overall, there was a high consensus rate on treatment approaches to control bleeding episodes. Regarding minor bleeding episodes, the experts did not

establish different administration regimens according to age group or type of FVIII used. The experts agreed on a single dose of 20-50 IU/kg to control mild joint bleeding, a regimen of 20-40 IU/kg for 1-3 days for mild muscular bleeding, a single dose of 20-40 IU/kg for episodes of mild bleeding in other areas (epistaxis, uncomplicated subcutaneous hematomas, small cuts, etc.), and no FVIII treatment or corticosteroid regimen to manage mild urological bleeds (moderate consensus) (Table 2). On the other hand, a bolus injection of

SHL rFVIII (70.8% to 92.6% agreement) or EHL rFVIII (100% agreement) should be administered to control a moderate or severe bleeding episode. In fact, there was a tendency to treat them intensively (every 12 h dosing) until the bleeding was resolved (3-5 days for joint bleeding; 7-10 days for muscle bleeding; 14 days for central nervous system bleeding and, 7-10 days for bleeding in other areas), except for urological bleeding. Therefore, consensus was not reached. To treat moderate or severe bleeding episodes, a slightly higher dosage was advised in pediatric patients (20-50 IU/kg) as compared to adult patients (20-35 IU/kg), and a longer administration interval was advised for pediatric patients when EHL rFVIII is used (every 8-12 h for SHL rFVIII and every 12-24 h for EHL rFVIII) (Table 2).

Surgical procedures

Regarding the prevention and bleeding control during surgical procedures, there was broad consensus on management regimens regarding major surgery. In the perioperative phase, regardless of the type of FVIII used (SHL or EHL), consensus was reached on the administration of a loading dose of 40-50 IU/kg for both pediatric and adult patients. No differences were observed between SHL rFVIII and nor EHL rFVIII administration after surgery (20-50 IU/kg every 8-12 h from day 1 to day 3 and 20-50 IU/kg every 12-24 h from day 4 were advised for pediatric patients, and 20-35 IU/kg every 8-12 h from day 1 to day 3 and 20-35 IU/kg every 12-24 h from day 4 were advised for adult patients) (Table 3).

Regarding minor surgery, no differences were observed in the administration schedule based on the type of FVIII administered. Consensus was reached on the administration of a loading dose of 30-40 IU/kg for both age groups, followed by 20-30 IU/kg or 20-40 IU/kg every 12-24 h for the first 2 days of treatment for pediatric patients and adult patients, respectively. No consensus was reached on treatment regimens after the third post operative day (Table 3).

Emicizumab

No consensus was reached regarding monitoring patients undergoing prophylactic treatment with emicizumab. Different approaches were given on the FVIII regimen needed to control bleeding episodes in these patients. As seen in the results after the two rounds of the questionnaire, general consensus was reached on the need of FVIII administration to treat joint, muscle

and urological hemorrhages (Table 4). Regarding surgical procedures, 90% of the experts agreed for FVIII administration before surgery. However, no consensus was reached regarding the postoperative administration regimen for patients treated with emicizumab (Table 4).

Discussion

Over the past few, the availability of new treatments for patients with hemophilia has increased. This study was developed to evaluate the real-life management of patients with severe HA without inhibitors regarding prophylaxis, treatment of bleeding episodes, and surgical approaches in different situations to establish practical recommendations for the management of these patients in Spain. A Delphi panel including hematologists experienced managing patients with hemophilia answered questionnaires in two rounds was created; 27 hematologists participated in the first round, and 24 hematologists in the second one.

The results of this study provide a clearly defined dosage regimen in the event of bleeding episodes and surgical procedures. Similarly, although experience using EHL rFVIII to treat patients with HA may be more limited, this study shows consensus was reached on the treatment regimens used to manage these patients with EHL rFVIII in different situations.

Regarding prophylaxis, the panelist achieved broad consensus on the recommendations for these patients according to the guidelines as seen on technical sheets and previous published data²⁴⁻³³. Of note the consensus obtained regarding the administration guideline does not always reflect the label. Recommendations for using EHL rFVIII to treat pediatric and adult patients included a longer interval administration compared to SHL. As this can lead to fewer IUs being administered, a lower economic impact of managing patients with HA could be seen afterwards. Different studies^{12,34} had also shown that reduction of the administration frequency significantly improves the patients' health-related quality of life of patients and, in turn, improves treatment compliance.

Consensus regarding the treatment regimen to control bleeding episodes was achieved. However, only moderate consensus was reached regarding mild urological bleeding. These results are understandable as clinical guidelines recommend abundant hydration (3 L/m²) for these 48 h avoiding the use of FVIII (1), but do not specify advised dosages according to bleeding severity^{35,36}.

Table 3. Results on the treatment of severe hemophilia A patients undergoing surgical procedures

	Response	Agreement	Result	Comments
Major surgery				
Would you administer a loading dose of 40-50 IU/kg?				
Pediatric patients on SHL rFVIII (n = 27)	YES	100.0%	Consensus 1 st round	-
Pediatric patients on EHL rFVIII (n = 27)	YES	100.0%	Consensus 1 st round	-
Adult patients on SHL rFVIII (n = 27)	YES	96.3%	Consensus 1 st round	-
Adult patients on EHL rFVIII (n = 27)	YES	96.3%	Consensus 1 st round	-
What administration regimen would the patient receive from day 1 to day 3?				
Pediatric patients on SHL rFVIII (n = 25)	20-50 IU/kg every 8-12 h	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Pediatric patients on EHL rFVIII (n = 25)	20-50 IU/kg every 8-12 h	91.7%	Consensus 1 st round	Responses were grouped to achieve consensus
Adult patients on SHL rFVIII (n = 24)	20-35 IU/kg every 8-12 h	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Adult patients on EHL rFVIII (n = 25)	20-35 IU/kg every 8-12 h	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
What administration regimen would the patient receive from day 4?				
Pediatric patients on SHL rFVIII (n = 24)	20-50 IU/kg every 12-24 h, 7-10 days	95.8%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Pediatric patients on EHL rFVIII (n = 24)	20-50 IU/kg every 12-24 h, 7-10 days	91.7%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Adult patients on SHL rFVIII (n = 24)	20-35 IU/kg every 12-24 h, 7-10 days	95.8%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Adult patients on EHL rFVIII (n = 24)	20-35 IU/kg every 12-24 h, 7-10 days	95.8%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Minor surgery				
Would you administer a loading dose of 30-40 IU/kg?				
Pediatric patients on SHL rFVIII (n = 27)	Yes	85.2%	Consensus 1 st round	-
Pediatric patients on EHL rFVIII (n = 25)	Yes	80.0%	Consensus 1 st round	-
Adult patients on SHL rFVIII (n = 27)	Yes	88.9%	Consensus 1 st round	-
Adult patients on EHL rFVIII (n = 27)	Yes	81.5%	Consensus 1 st round	-
What administration regimen would the patient receive from day 1 to day 2?				
Pediatric patients on SHL rFVIII (n = 26)	20-30 IU/kg every 12-24 h	88.5%	Consensus 1 st round	Responses were grouped to achieve consensus
Pediatric patients on EHL rFVIII (n = 26)	20-30 IU/kg every 12-24 h	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Adult patients on SHL rFVIII (n = 26)	20-40 IU/kg every 12-24 h	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
Adult patients on EHL rFVIII (n = 25)	20-40 IU/kg every 12-24 h	100.0%	Consensus 1 st round	Responses were grouped to achieve consensus
What administration regimen would the patient receive from day 3?				
Pediatric patients on SHL rFVIII (n = 24)	20-30 IU/kg every 12-24 h, 3-5 days	75.0%	Moderate consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Pediatric patients on EHL rFVIII (n = 24)	No consensus			
Adult patients on SHL rFVIII (n = 24)	No consensus			
Adult patients on EHL rFVIII (n = 24)	No consensus			

SHL rFVIII: standard half-life recombinant FVIII; EHL rFVIII: extended half-life recombinant FVIII.

Table 4. Results on emicizumab prophylactic treatment of patients with severe hemophilia A

	Response	Agreement	Result	Comments
Prophylactic treatment				
Would you recommend monitoring?				
Adult patient with emicizumab (n = 23)	No consensus			
Mild joint bleeding				
Would you treat the patient with FVIII?				
Adult patient with emicizumab (n = 24)	Yes	91.7%	Consensus 2 nd round	-
What administration regimen would the patient receive?				
Adult patient with emicizumab (n = 23)	No consensus			
Moderate/severe joint bleeding				
Would you administer a loading dose of 35-50 IU/kg?				
Adult patient with emicizumab (n = 24)	Yes	91.7%	Consensus 2 nd round	-
What administration regimen would the patient receive?				
Adult patient with emicizumab (n = 24)	15-25 IU/kg every 24 h, > 5 days	91.6%	Consensus 2 nd round	-
Mild muscle bleeding				
Would you treat the patient with FVIII?				
Adult patient with emicizumab (n = 24)	Yes	75.0%	Moderate consensus 2 nd round	-
What administration regimen would the patient receive?				
Adult patient with emicizumab (n = 24)	< 20 IU/kg every 12-24 h, 3-5 days	70.8%	Moderate consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Moderate/severe muscle bleeding				
Would you administer a loading dose of 35-50 IU/kg?				
Adult patient with emicizumab (n = 24)	Yes	95.8%	Consensus 2 nd round	-
What administration regimen would the patient receive?				
Adult patient with emicizumab (n = 24)	15-25 IU/kg every 24 h, 3-5 days	95.8%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Mild urological bleeding				
Would you initially treat the patient with FVIII?				
Adult patient with emicizumab (n = 24)	No	87.5%	Consensus 1 st round	-
Would you administer a corticosteroid regimen?				
Adult patient with emicizumab (n = 23)	No	73.9%	Moderate consensus 2 nd round	-

(Continues)

Table 4. Results on emicizumab prophylactic treatment of patients with severe hemophilia A (*continued*)

	Response	Agreement	Result	Comments
Moderate/severe urological bleeding				
Would you administer a loading dose of 35-50 IU/kg?				
Adult patient with emicizumab (n = 24)	Yes	87.5%	Consensus 2 nd round	-
What administration regimen would the patient receive?				
Adult patient with emicizumab (n = 11)	15-25 IU/kg every 24 h, 3-5 days	81.8%	Consensus 1 st round	-
Moderate/severe central nervous system bleeding				
Would you administer a loading dose of 35-50 IU/kg?				
Adult patient with emicizumab (n = 16)	Yes	100.0%	Consensus 1 st round	-
What administration regimen would the patient receive?				
Adult patient with emicizumab (n = 24)	No consensus			
Mild bleeding in other areas				
Would you initially treat the patient with FVIII?				
Adult patient with emicizumab (n = 24)	No	75.0%	Moderate consensus 2 nd round	-
What administration regimen would the patient receive?				
Adult patient with emicizumab (n = 4)	< 20 IU/kg, single dose	100.0%	Consensus 1 st round	-
Moderate/severe bleeding in other areas				
Would you administer a loading dose of 35-50 IU/kg?				
Adult patient with emicizumab (n = 24)	Yes	95.8%	Consensus 2 nd round	-
What administration regimen would the patient receive?				
Adult patient with emicizumab (n = 24)	15-25 IU/kg every 12-24 h, 3-5 days	91.7%	Consensus 2 nd round	Responses were grouped to be reconsidered in the second round
Major surgery				
In the perioperative phase, would you administer FVIII?				
Adult patient with emicizumab (n = 20)	Yes	90.0%	Consensus 1 st round	-
Would you administer a loading dose of 35-50 IU/kg?				
Adult patient with emicizumab (n = 16)	Yes	87.5%	Consensus 1 st round	-
What administration regimen would the patient receive?				
Adult patient with emicizumab (n = 22)	No consensus			

(Continues)

Table 4. Results on emicizumab prophylactic treatment of patients with severe hemophilia A (*continued*)

	Response	Agreement	Result	Comments
Minor surgery				
In the perioperative phase, would you administer FVIII or antifibrinolytic?				
Adult patient with emicizumab (n = 24)	No consensus			
Would you administer a loading dose of 25-35 IU/kg?				
Adult patient with emicizumab (n = 24)	No consensus			
What administration regimen would the patient receive?				
Adult patient with emicizumab (n = 5)	< 20 IU/kg every 24 h, 1-3 days	100.0%	Consensus 1 st round	-
Pediatric patient				
Would you consider the administration regimen used applicable to the pediatric population?				
Pediatric patient with emicizumab (n = 24)	Yes	70.8%	Moderate consensus 2 nd round	-

FVIII: factor VIII.

Consensus was reached regarding treatment administration during major surgery, during the perioperative phase and the early and late post operative periods. No consensus was ever reached on treatment regimens on the 3rd or 4th days after a surgical procedure except for pediatric patients treated with SHL rFVIII. For them, a moderate consensus was reached on an administration regimen of 20-30 IU/kg every 12-24 h for 3-5 days. The lack of consensus may be related to the different types of surgical procedures (dental extractions, endoscopic procedures, insertion of central venous access devices, etc.). Therefore, depending on the surgical intervention and its specific bleeding risk, a different administration regimen will be chosen depending on previous experience. In addition, treatment may also change depending on the outcomes.

The participants reached no consensus at all regarding the administration of FVIII for bleeding episodes in adult patients with severe HA without inhibitors and on prophylactic treatment with emicizumab. The lack of a consensus may be due to the limited experience clinicians have with emicizumab in the routine clinical practice.

This study has a series of limitations that should be taken into consideration, most of them intrinsic to the use of a Delphi method. The modified Delphi method resulted in a limited number of answers, a potential bias induced by the used of pre-established questions and the impossibility to know the opinion of each panelist³⁷. To minimize this, all the proposed answers as well as the results of the first questionnaire were shared during the second

round. Another possible limitation is the influence of organizers. This influence might occur in the selection of the scientific committee and during the discussion of the results. However, these limitations cannot be fully resolved because HA is a disease treated mostly in reference centers and there is a very limited number of experts in the field. In addition, the results were analyzed by an external entity to reduce this bias. Another limitation relies on applying the questionnaire to a smaller number of experts in the second round since the response rate was lower. However, previous studies have mentioned that the optimal number of participants should be between 7 and 30 participants as a higher number does not increase the validity of the Delphi method but may increase its complexity and associated costs^{38,39}.

Despite of all these limitations, the results shown in this study clarify what the preferred approaches regarding prophylaxis, control of different types of bleeding episodes and perioperative management both pediatric and adult patients with severe HA really are. These approaches are of great interest to hematologists, pediatricians, and other health care professionals, involved in the management of patients with hemophilia who require very specific management.

Conclusions

In conclusion, this study shows that there is large consensus on the management of SHL FVIII or EHL in

patients with severe hemophilia A in Spain. This Delphi method indicates that the administration of EHLs as prophylactic treatment is spaced out in both children and adults compared to the administration of SHL FVIII. Therefore, regarding bleeding episodes, EHL rFVIII are controlled with a more spaced treatment schedule (12-24h) than SHLs (8-12h). These results could be of interest to haematologists, paediatricians and other healthcare professionals involved in the treatment of hemophilia patients who require very specific treatment.

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Conflicts of interest

M^a. Teresa Álvarez-Román, Rubén Berruero, M. Saturnino Haya, Ana Moretó, and Manuel Rodríguez received consultancy fees for participating in the Delphi project. M^a. Teresa Álvarez-Román has been a consultant and received fees from Bayer, CSL Behring, Amgen, Novartis, Sobi, Novo Nordisk, Takeda, and Roche. Rubén Berruero has been a consultant for Bayer, CSL Behring, and Novartis and received fees from CSL Behring, Novartis, Bayer, Sobi, Novo Nordisk, Takeda, and Roche. M. Saturnino Haya has received fees as a speaker at several meetings organized by Baxter, Shire, Sobi, Grifols, Novo Nordisk, and Pfizer and received fees for consultancy jobs for Grifols and Shire. Ana Moretó has received fees as a speaker at several meetings for Novartis, Novo Nordisk, Sobi, Pfizer, CSL Behring, Roche, Sanofi and Leo-Pharma, and been a consultant for Amgen, Shire, Sobi and Novo Nordisk. Miguel Ángel Casado, and María Mareque are employees of PORIB, a company that received funding from Swedish Orphan Biovitrum S.L. to coordinate and conduct the project and for medical writing services.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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