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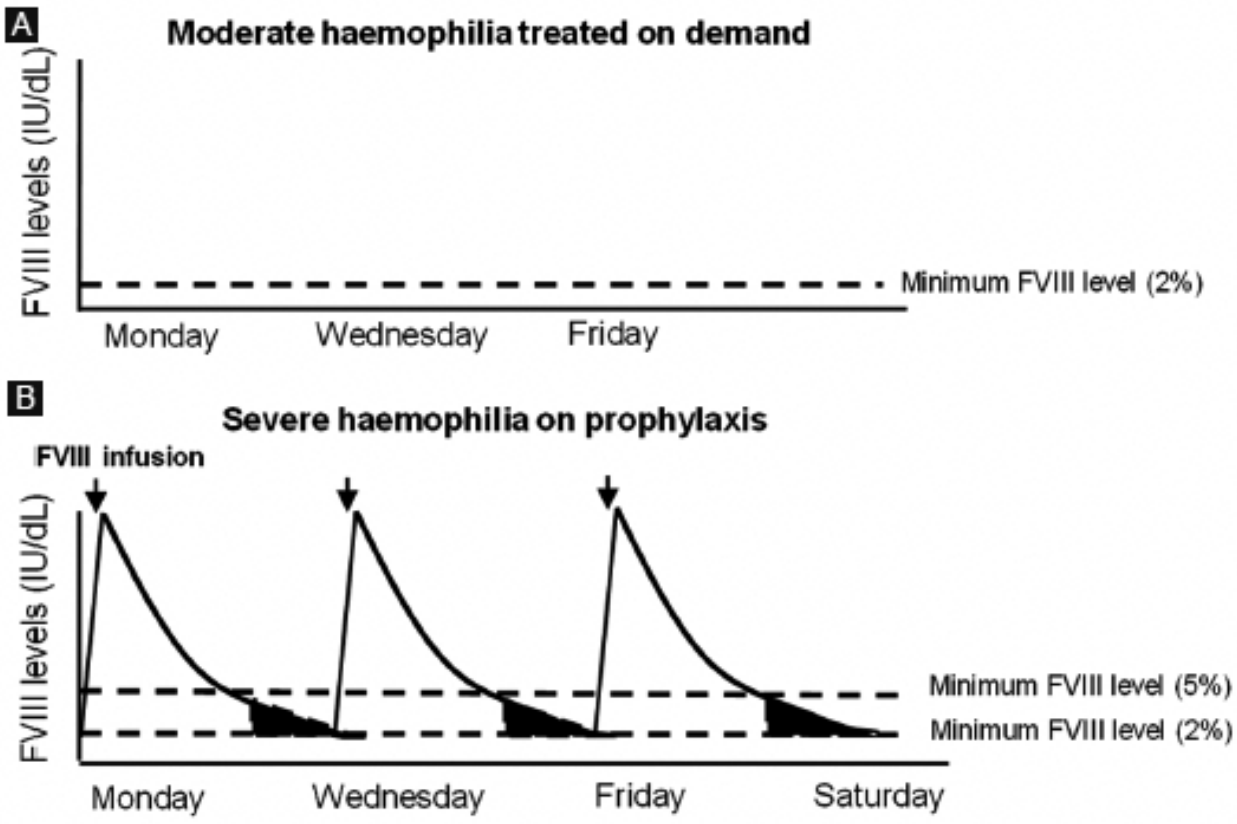

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EDITORIAL

Beyond the factor: the present of hemophilia as innovation in medicine

Más allá del factor: el hoy de la hemofilia como innovación en medicina

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The study and clinical practice of hemostasis are undergoing a profound transformation. In this field, hemophilia is one of the most dynamic and innovative areas of contemporary medicine. Few areas have experienced, in such a short time, such an intense convergence of advances in molecular biology, pharmacological development, and changes in the care model. In just a few decades, the management of this disease has evolved from on-demand replacement of coagulation factors in response to bleeding toward highly effective prophylactic strategies, non-replacement therapies capable of rebalancing the hemostatic system, and gene therapy approaches that aim for prolonged functional correction of the molecular defect. These innovations have not only radically improved patient prognosis, but have also turned hemophilia into a model for the development and evaluation of new therapeutic strategies.

This scientific progress has redefined treatment goals. The objective is no longer limited to controlling bleeding and limiting progressive joint damage; rather, it aims at something far more ambitious: preserving normal joint function from childhood, ensuring a quality of life comparable to that of the general population, and, in some cases, achieving prolonged functional correction of the coagulation defect. The speed at which innovations are emerging also raises new challenges for clinical practice, including the evaluation of long-term treatment safety and the integration of new practices into healthcare systems. Therefore, analyzing and implementing the adaptation of care models in a sustainable manner is currently a central issue.

In this context, the work by Rodríguez-López et al.,[1] focused on the indirect comparison of different gene therapies in hemophilia A, illustrates both the potential of these strategies and the uncertainties that still remain. The data show favorable results in factor VIII levels and reduction of bleeding episodes, but also reveal relevant differences between therapeutic platforms in terms of stability, safety profile, and the need for immunosuppression. Overall, gene therapies in hemophilia A are promising, but they need improvement in certain aspects to reach the levels achieved in gene therapy for hemophilia B. Beyond the results, this study introduces the exploratory use of generative artificial intelligence as a tool to support analysis. This approach represents a transformation in how clinical evidence is analyzed, but at the same time underscores the need to maintain methodological rigor and clinical judgment as fundamental pillars of scientific interpretation.

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If gene therapy represents innovation, prophylaxis remains the core of clinical practice, and the development of inhibitors is a serious risk, especially in previously untreated patients. In this issue, the RePUM-HA registry is presented: a Spanish registry of routine clinical practice in previously untreated or minimally treated patients with severe hemophilia A. This registry is an initiative of the *Sociedad Española de Trombosis y Hemostasia* and aims to investigate the safety and efficacy profile of replacement and non-replacement treatments in the prophylaxis of these patients, in a study that will extend from 2021 to 2028, with a retrospective phase and a prospective phase, now underway. The dissemination of high-quality registries, which provide a complementary perspective to that of clinical trials, is one of the strategic priorities of our journal, which seeks to contribute to their development. For their part, Del Estal-Jiménez et al.[2] present the clinical case of a patient with hemophilia B who developed an inhibitor that could not be eliminated with immune tolerance therapies using standard half-life factor IX concentrates, but who responded to treatment with extended half-life concentrates bound to recombinant albumin. This case report suggests that the use of extended half-life products could improve clinical outcomes in patients with difficult-to-treat factor IX inhibitors.

However, innovation is not limited to the development of new therapies. The article by Núñez-Vázquez et al.[3] reviews the current role of prophylaxis in hemophilia A in a context of increasing therapeutic complexity. The authors highlight the need to move beyond the classical approach based exclusively on plasma factor VIII levels, proposing as the real clinical objective the absence of bleeding and the preservation of joint function. They emphasize that prophylaxis must be individualized according to the bleeding phenotype and patient characteristics, adapting therapeutic regimens to the patient's profile and clinical context. This approach reinforces the idea that innovation also lies in improving existing strategies, not only in introducing new technologies. Overall, the article advocates for a more physiological prophylaxis, focused on clinical outcomes rather than solely on pharmacokinetic parameters.

In contrast to technological and pharmacological advances, the work by Pasquero et al.[4] introduces an essential and sometimes overlooked dimension of clinical management: the central role of the patient in their disease. The study on disease awareness demonstrates that knowledge of diagnosis and treatment directly influences therapeutic adherence and clinical outcomes. Patients with greater disease awareness show better adherence to prophylaxis, fewer bleeding episodes, and better preservation of joint function. Their study demonstrates that simple educational interventions implemented systematically can lead to clear improvements in care. This highlights that while technological innovation advances rapidly, human factors remain equally relevant for therapeutic success.

Taken together, the articles included in this issue outline a coherent and representative overview of the current state of hemophilia, from gene therapy to clinical registries, from inhibitor development to the optimization of prophylaxis and therapeutic adherence. Ultimately, the challenge lies in integrating these increasingly sophisticated advances into coherent, equitable, sustainable, and patient-centered clinical practice. Hemophilia, now more than ever, is engaged in the search for this balance between innovation and clinical and social responsibility, offering lessons that extend beyond its own field and are applicable to medicine as a whole.

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ORIGINAL RESEARCH ARTICLE

Spanish registry of real-world clinical practice in previously untreated or minimally treated patients with severe hemophilia A (RePUM-HA)

Registro español de práctica clínica habitual en pacientes con hemofilia A grave previamente no tratados o mínimamente tratados (RePUM-HA)

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Abstract

Introduction: *The development of inhibitors against factor VIII remains a significant complication in hemophilia A, especially in previously untreated patients. Non-replacement therapies have enabled the initiation of primary prophylaxis at very early stages, although uncertainties persist regarding the risk of inhibitor development after late factor VIII exposure, the choice of concentrate, and tolerization strategies.* **Objective:** *The aim of the RePUM-HA registry is to generate real-world evidence to better understand and reach consensus on the management of these patients in our country.* **Material and method:** *National, multicenter, observational registry running from 2021 to 2028, including previously untreated and minimally treated patients (< 5 exposure days) with severe or moderate hemophilia A, under 3 years of age, without inhibitors, who started prophylaxis after 2020. Clinical, genetic, therapeutic, bleeding, immu-nogenicity, and adverse event data will be collected.* **Results:** *Approximately 50 patients are expected to be enrolled to assess inhibitor risk, clinical outcomes, and prophylactic regimens in real-world practice.* **Conclusions:** *This study will provide evidence to optimize strategies and inform future national recommendations.*

Keywords: *Hemophilia. Previously untreated patient. Prophylaxis. Therapy. Inhibitors.*

Resumen

Introducción: *El desarrollo de inhibidores frente al factor VIII sigue siendo una complicación relevante en la hemofilia A, especialmente en pacientes previamente no tratados. Los tratamientos no sustitutivos han permitido iniciar la profilaxis primaria en etapas muy precoces, aunque persisten dudas sobre el riesgo de inhibidores tras la exposición tardía a factor VIII, la elec-ción del concentrado y las estrategias de tolerización.* **Objetivo:** *El objetivo del registro RePUM-HA es generar evidencia de la vida real que permita conocer y consensuar el manejo de estos pacientes en nuestro país.* **Material y métodos:** *Registro observa-*

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cional, multicéntrico y nacional, entre 2021 y 2028, que incluye pacientes previamente no tratados y mínimamente tratados (< 5 días de exposición) con hemofilia A grave o moderada, menores de 3 años, sin inhibidores, que comenzaron la profilaxis a partir de 2020. Se recogerán datos clínicos, genéticos, terapéuticos, sangrados, inmunogenicidad y eventos adversos. **Resultados:** *Se prevé incluir unos 50 pacientes para evaluar el riesgo de inhibidores, los resultados clínicos y los esquemas profilácticos en la práctica real.* **Conclusiones:** *Este estudio aportará evidencia para optimizar estrategias y futuras recomendaciones nacionales.*

Palabras clave: *Hemofilia. Paciente previamente no tratado. Profilaxis. Tratamiento. Inhibidor.*

Introduction

Hemophilia A is an X-linked congenital disorder characterized by a impairment in the synthesis or function of factor VIII (FVIII) and an associated variable bleeding phenotype, generally related to the severity of the deficiency.[1] The presence of a family history may allow prenatal diagnosis; however, in sporadic cases, the disease is diagnosed after a first bleeding event following birth or during the first months of life.[2] One of the most feared bleeding events within the first year of life is intracranial hemorrhage. Its incidence is 2.1 events per 100 deliveries in patients with hemophilia, and this risk also persists during the first 12 months of life, especially in patients who do not receive prophylactic treatment.[3,4]

Prophylaxis has proven being effective in reducing bleeding events in patients with hemophilia, but the initiation of replacement therapy with FVIII in very young patients entails several challenges.[5,6] On the one hand, periodic IV administration may require placement of a central venous catheter, given the difficulty of accessing peripheral veins in infants, especially those < 3-6 months. On the other hand, exposure to FVIII in previously untreated patients (PUP) with hemophilia A leads to the development of neutralizing antibodies (inhibitors) against FVIII in 25-40% of cases.[7] A total of 79% of inhibitors develop during the first 20 exposures to FVIII, but the risk persists for at least up to 75 exposures.[7] The development of inhibitors is a serious complication, as they neutralize factor activity and reduce its efficacy, increase patient morbidity and mortality, and worsen quality of life.[8,9] It has been described that controlled and regular exposure to FVIII in a prophylactic regimen, especially when initiated early, may reduce the risk of inhibitor development.[7] However, the existence of other risk factors is well known, such as family history of inhibitors, the need for intensive treatment during the first administrations, or the causative mutation of the disease.[2,10] In fact, more than 70% of mutations leading to severe forms of hemophilia A are associated with a high risk of inhibitor development.[7]

Emicizumab is a recombinant, humanized, bispecific monoclonal antibody approved for prophylaxis in patients with hemophilia A, with or without inhibitors, of all ages. It exerts its action by mimicking the function of FVIII, acting as a bridge between activated factor IX and factor X to activate the latter, and is administered subcutaneously on a weekly regimen or every 2 or 4 weeks.[11] Initial registration studies demonstrated that emicizumab is safe and effective in preventing bleeding in patients with hemophilia A > 1 year;[12] however, there were concerns regarding its efficacy in very young children, as factors XI and X have physiologically lower levels compared to adults.[13] The HAVEN-7 study demonstrated the safety and efficacy profile of emicizumab as prophylactic treatment in 55 patients with hemophilia A younger than 1 year. In fact, no patient experienced intracranial hemorrhage after initiating treatment at a mean age of 5 months (compared with the previously reported 13.1 months).[14] These results have made it possible to consider initiation of primary prophylaxis at an earlier age, immediately after diagnosis.[12]

However, this therapy also presents several limitations. Prophylaxis with emicizumab reduces spontaneous and severe bleeding, but the risk of bleeding does not completely disappear, as described in all HAVEN registration studies and in other real-world studies.[11,15-17] These bleeding episodes may require administration of FVIII concentrates which, in PUP and minimally treated patients (MTP), could result in the development of inhibitors.[12] Nevertheless, prophylaxis with emicizumab may alter the "natural" course of inhibitor development associated with conventional replacement therapy. Prophylaxis with replacement therapy implies that newborns and infants with severe hemophilia A require a mean of 1.2 years to reach 75 exposures. However, patients on emicizumab may require much longer, even years, to reach those 50-75 exposures.[12,18] Although age does not appear to be a key factor in the risk of inhibitor development, the financial impact of inducing immune tolerance in older children is considerably higher. Therefore, there are many

uncertainties regarding several issues, such as whether regular exposure to FVIII is necessary in patients with hemophilia A initiating prophylaxis with emicizumab. The lack of consensus in the scientific community was highlighted in a survey conducted in 32 centers belonging to PedNet.[8] In 20 of 25 centers, emicizumab was the preferred option to initiate prophylaxis in PUP and MTP, and in most cases (80%), FVIII was not administered concomitantly. Another controversy concerns the type of FVIII that should be used, especially with the emergence of new extended and ultra-extended half-life products not included in the SIPPET study.[19] There are also no recommendations regarding which treatment to continue once those first 20-50 exposures have been reached.[5] The objective of the RePUM-HA registry is to generate real-world evidence to better understand and standardize the management of these patients in Spain.

Method

Study design

We conducted an observational, multicenter study with retrospective data collection (from January 2021 through October 2025) and prospective data collection (from October 2025 through December 2028) in PUP and MTP patients with severe and moderate hemophilia A without inhibitors who initiate prophylactic treatment during the study period in Spain. This registry is part of the initiatives of the Sociedad Española de Trombosis y Hemostasia.

Endpoints

- Primary endpoint**:** to investigate the safety and efficacy of replacement and non-replacement therapies used as prophylaxis in PUP or MTP patients with severe hemophilia A (FVIII: C ≤ 1%) or moderate hemophilia A (FVIII: C > 1 to ≤ 5%) without inhibitors during routine clinical practice in a single country.
- Secondary endpoints: to evaluate the rate of inhibitor development during the study period in a series of PUP and MTP patients on prophylactic treatment.
  - To evaluate the annual bleeding rate in a series of PUP and MTP patients on prophylaxis during the study period, analyzing episodes requiring treatment administration.
  - To evaluate different therapeutic and follow-up approaches in relation to the initial FVIII tolerization regimen, bleeding management, and surgical management, with the aim of designing and implementing uniform and consensus-based treatment strategies across different centers in Spain.

Inclusion and exclusion criteria

- Inclusion criteria:
  - Patients diagnosed with severe (FVIII < 1%) or moderate (FVIII 1-5%) hemophilia A without inhibitors at study initiation.
  - PUP patients (1-2 exposures) or MTP patients (3-5 exposures) who initiated primary prophylaxis after January 1, 2020.
  - Age < 3 years at the time of prophylaxis initiation.
  - Complete records of treatment administration, bleeding episodes, administration of coagulation factor for bleeding management, and periodic inhibitor assessment.
  - Signed informed consent from parents, caregivers, or legal guardians.
- Exclusion criteria:
  - Patients who do not meet inclusion criteria at the time of prophylaxis initiation.
  - Patients who developed inhibitors prior to starting prophylaxis.
  - Patients for whom informed consent cannot be obtained.
  - Patients participating in a clinical trial involving replacement or non-replacement therapy.

Sample size calculation

The annual number of male newborns in Spain has been approximately 320,000 in recent years, of whom around 170,000 are male. The incidence rate of hemophilia A is 1 per 5,000 live male births, and that of severe hemophilia A is approximately 1 per 16,000; it is estimated that 15% of patients with hemophilia A have a moderate form. Based on these data, we estimate approximately 10 patients with severe hemophilia A per year and 5 patients with moderate hemophilia A per year.

Considering that this registry includes a geographically representative sample of centers across Spain (Table 1 of the Supplementary Data), including the main referral units and the four CSUR centers, as well as the fact that not all patients with moderate hemophilia A will receive prophylaxis, we estimate a total of 12 patients per year, resulting in a minimum of 50-60 patients by the end of the study.

Recruitment and ethical aspects

Recruitment and the consent process will be carried out during routine follow-up visits at the referral hemophilia unit. Due to the age of the patients, their parents or legal guardians will be informed about the study. After signing the informed consent, clinical data will be collected from the medical records. Patients and their caregivers will not undergo any tests or questionnaires beyond those used in routine clinical practice.

Results

The expected results of this study will address the primary endpoint of evaluating safety (development of inhibitors) and efficacy (annual bleeding rate) of replacement and non-replacement prophylactic treatment in PUP or MTP patients with severe (FVIII ≤ 1%) or moderate (FVIII > 1 to ≤ 5%) hemophilia A without inhibitors. Secondary objectives include bleeding and surgical management, as well as the effects of tolerization strategies.

Variables

Clinical data will be collected by the investigator in a specific study data collection form, which will be pseudo-anonymized to protect patient identity. The following will be recorded:

- Demographic data: age (calculated in months) and sex.
- Medical history:
  - Severity level of hemophilia: moderate or severe.
  - Genetic diagnosis: information related to the detected mutation.
  - Family history of FVIII inhibitors.
- Treatment history:
  - Number of prior FVIII exposures: this value must not exceed 5.
  - Reason for prior administration of each FVIII dose received.
  - Type of FVIII administered.
- Prophylactic treatment:
  - Age at initiation of prophylactic treatment.
  - Dose and regimen of the administered treatment.
  - Main reason for treatment choice: patient or caregiver preference, treating team preference, prevention of inhibitor development in high-risk patients, bleeding prevention, or others.
- Follow-up and evaluation (minimum data collection every 12 months, preferably every 6 months):
  - Age at follow-up.
  - Weight and height.
  - Dose and treatment regimen.
- Treatment efficacy:
  - Patient age at the time of bleeding episode.
  - Bleeding episodes and information regarding spontaneous or traumatic bleeding, location, severity, administered treatment, hospital admission, and additional follow-up visits.
- Safety and tolerability:
  - Treatment-related adverse events: adverse events and serious adverse events will be reported according to protocol.
  - Development of inhibitors: age at diagnosis and number of prior FVIII exposures; inhibitor titer at diagnosis.
  - Treatment adherence.
- Medical interventions:
  - Surgeries or other invasive procedures performed during follow-up.
  - Patient age at the time of surgery or invasive procedure.
  - FVIII administration (if required), number of administrations, and dose.
- Joint health (if available):
  - Clinical assessment scale (Hemophilia Joint Health Score [HJHS]).
  - Ultrasound joint assessment scale (Hemophilia Early Arthropathy Detection with Ultrasound [HEAD-US]).

Definitions

- Severe hemophilia A: FVIII deficiency < 1%.[20]
- Moderate hemophilia A: FVIII deficiency 1-5%.[20]
- Previously untreated patient (PUP): patient who has not received FVIII or has received only 1 or 2 doses.
- Minimally treated patient (MTP): patient who has received 3 to 5 doses of FVIII.
- Inhibitors: presence of neutralizing antibodies against FVIII determined according to the modified Bethesda method, with a value > 0.6 Bethesda units.
- Assessment of treatment adherence: good (80-100%), moderate (65-80%), or poor (< 65%), determined based on patient-reported information or indirect pharmacy records.

Analysis of results

A descriptive analysis of the entire series and of the results in relation to the primary and secondary

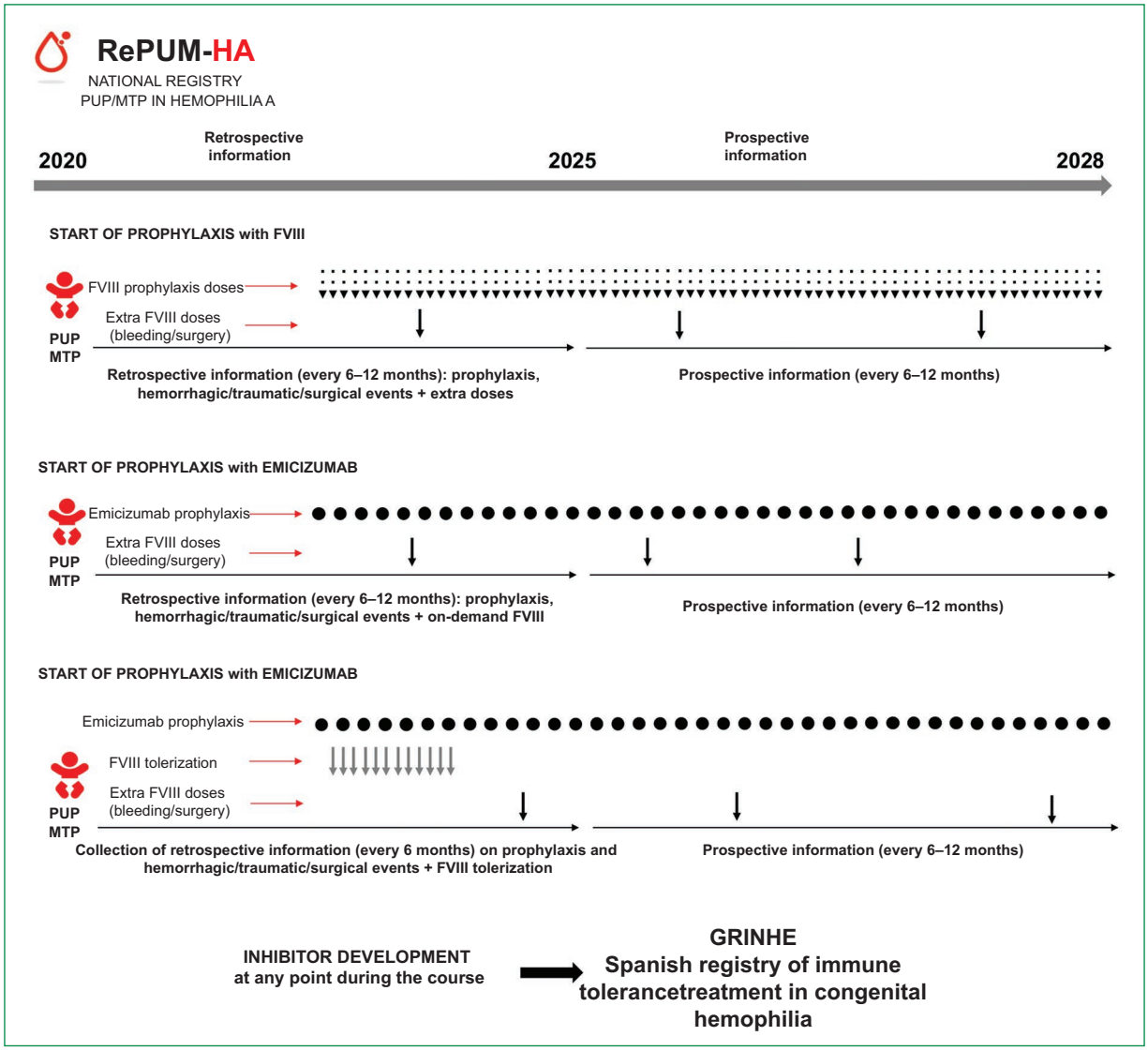

Figure 1. Scheme of retrospective and prospective data collection in the study according to the type of treatment with which prophylaxis was initiated, the use of FVIII doses for tolerization, or the use of FVIII as additional doses.

endpoints will be conducted. Subsequently, results will be analyzed by classifying patients into different subgroups. The following assumptions are proposed: 1) type of prophylaxis received; 2) severity of hemophilia; 3) PUP or MTP patients; 4) causative mutation of the disease; and 5) patients receiving emicizumab who have (or have not) undergone FVIII tolerization.

Statistical analysis

A descriptive analysis of the main study variables will be performed. For qualitative variables, results will be expressed as frequency, percentage, and confidence interval. For quantitative variables, mean and SD, and median with IQR, will be reported. Statistical analyses will include comparison of frequencies of categorical variables between groups using the chi-square or Fisher's exact test. For comparison of quantitative variables between groups, Student's t test will be used in case of normal distribution, and the nonparametric Mann-Whitney U test if the distribution is not normal. To compare quantitative variables within the same subjects at different time points, paired Student's t test will be used in case of normal distribution, and the nonparametric Wilcoxon test in case of non-normal distribution. Results will be considered statistically significant when $p < 0.05$. Statistical analyses will be performed using SPSS v23.0 (IBM Corp, Armonk, NY, USA).

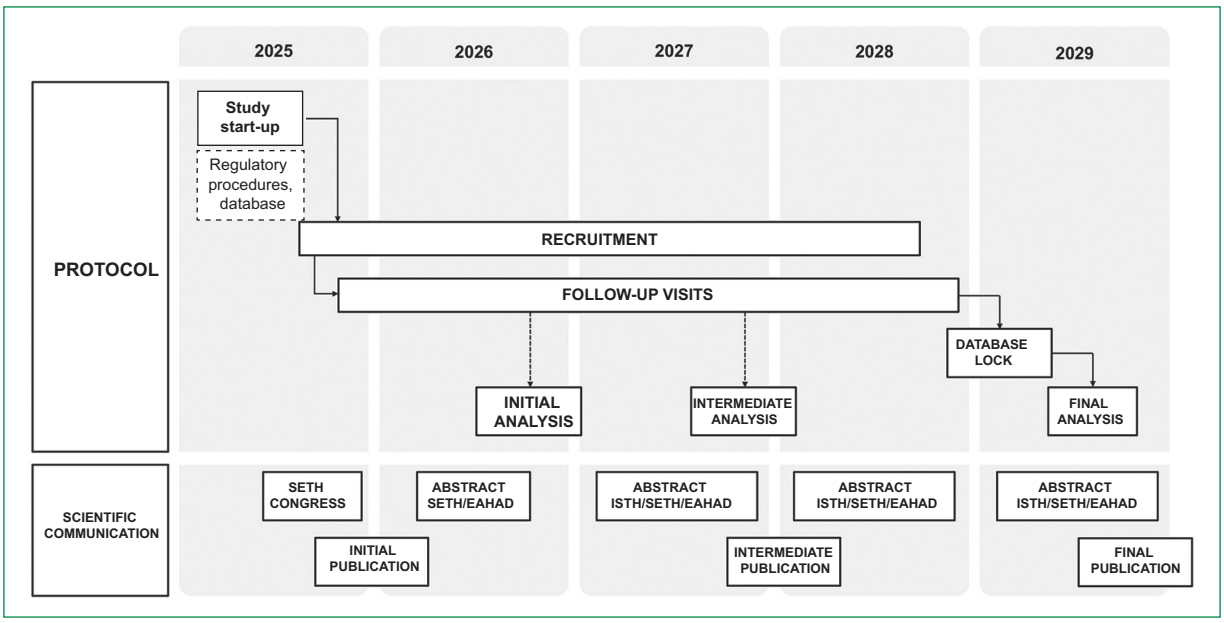

Figure 2. Work timeline.

Ethical aspects

The study will be conducted in accordance with the Declaration of Helsinki (2024) on ethical principles for medical research involving human subjects, Royal Decree 1090/2015 of December 24 on clinical trials, specifically the provisions of Article 38 on good clinical practice, and the Convention on Human Rights and Biomedicine, signed in Oviedo on April 4th, 1997, and its subsequent updates.

Patients, parents, or legal representatives will sign informed consent for inclusion in the registry. The study has been evaluated by the CEIm of the Fundación Sant Joan de Déu (EOM-02-25).

Safety reporting

Local investigators will report, in accordance with applicable legal obligations, and study data will be collected on all adverse events, including inhibitors, allergic reactions, thromboembolic complications, thrombotic microangiopathic complications, and deaths suspected to be related to hemophilia treatment. Reports on non-replacement therapies will include data on any other adverse events, as appropriate. Non-serious adverse events will be recorded according to the appropriate MedDRA classification level. Annual reports of all reported inhibitors will be prepared, correlated with the products used. Data reports will be sent to all participating centers and sponsors in relation to their products. Safety reporting for registered products will be carried out by participating centers in accordance with national regulations established by competent authorities.

Timeline and current status

The first patient was recruited in September 2025. Data collection is expected to continue for the next 3 years (until study completion) (Fig. 1). Results, analyzed annually, will be presented at scientific meetings and published in indexed journals. All publications and presentations related to the study will be authorized and reviewed by all investigators. The project timeline is shown in figure 2.

Conclusions

RePUM-HA represents a unique opportunity to understand the impact of new prophylactic strategies in PUP and MTP patients in routine clinical practice in our country. The collected information will help address still unanswered questions, such as the timing and type of FVIII exposure, the need to design tolerization protocols, and the economic and clinical impact of new therapies. This registry aims to lay the groundwork for future national recommendations and to promote

collaboration among centers and, subsequently, with other international groups.

Funding

The study sponsor is the Fundación Española de Trombosis y Hemostasia, and the registry is funded by Roche.

Conflicts of interest

R. Berrueco has received contract support from Roche, reimbursement for conference attendance, honoraria for lectures and consultancy, and research funding from Takeda, Roche, Bayer, CSL-Behring, Novo Nordisk, Sobi, Octapharma, Amgen, Werfen, Stago, Boehringer Ingelheim, and Pfizer. M.T. Álvarez-Román has participated as a speaker, in advisory boards, and in symposia sponsored by Novo Nordisk, Takeda, Roche, Pfizer, Octapharma, Amgen, Novartis, CSL Behring, and Sobi. M. Rodríguez-López has received reimbursement for conference attendance and honoraria for lectures and consultancy from Octapharma, Sobi, Roche, CSL Behring, Amgen, Takeda, Novo Nordisk, Pfizer, Grifols, and LFB. V. Jiménez-Yuste has received support and contracts from F. Hoffmann-La Roche Ltd, Novo Nordisk, Sobi, Takeda, Grifols, Bayer, Pfizer, Octapharma, and CSL Behring, as well as honoraria for lectures, presentations, manuscript writing, and educational events from F. Hoffmann-La Roche Ltd, Novo Nordisk, Sanofi, Sobi, Takeda, Grifols, Bayer, Pfizer, Spark Therapeutics, BioMarin, Octapharma, and CSL Behring. R.J. Núñez-Vázquez has received honoraria for lectures and advisory board participation from Roche, CSL Behring, Sobi, Octapharma, Novo Nordisk, Takeda, and Pfizer, as well as support for meeting attendance from Octapharma, Roche, and Sobi.

Ethical considerations

Protection of persons and animals. The authors declare that no experiments involving humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their healthcare institution's protocols for accessing clinical record data. Informed consent has been obtained from patients, and approval from the Ethics Committee has been secured. SAGER guidelines have been followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

Supplementary data

Supplementary data is available at 10.24875/RHT.25000022. This material is provided by the corresponding author and published online for the benefit of the reader. The content of the supplementary material is the sole responsibility of the authors.

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ORIGINAL RESEARCH ARTICLE

Disease awareness in hemophilia: impact on therapeutic adherence and clinical outcomes

Conciencia de enfermedad en hemofilia: impacto en la adherencia terapéutica y los resultados clínicos

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Abstract

Introduction: *Hemophilia is an inherited bleeding disorder that requires multidisciplinary management to reduce long-term complications. Disease awareness may influence treatment adherence and clinical outcomes.* **Objective:** *To analyze the relationship between disease awareness and adherence to prophylactic therapy in patients with hemophilia.* **Material and methods:** *A review of assessment tools and strategies addressing psychosocial, educational, and economic barriers to adherence was conducted.* **Results:** *Higher disease awareness was associated with improved adherence, reduced bleeding episodes, and better preservation of joint function.* **Conclusions:** *Disease awareness is a key determinant of adherence in patients with hemophilia. Interventions that enhance patient self-management may improve long-term health outcomes.*

Keywords: *Hemophilia. Health knowledge. Treatment adherence.*

Resumen

Introducción: *La hemofilia es un trastorno hemorrágico hereditario que requiere manejo multidisciplinario para reducir las complicaciones a largo plazo. La conciencia de enfermedad podría influir en la adherencia terapéutica y en los resultados clínicos.* **Objetivo:** *Analizar la relación entre la conciencia de enfermedad y la adherencia al tratamiento de profilaxis en pacientes con hemofilia.* **Material y método:** *Se revisaron herramientas de evaluación y estrategias orientadas a superar barreras psicosociales, educativas y económicas que afectan a la adherencia.* **Resultados:** *Una mayor conciencia de enfer-medad se asoció con mejor adherencia, menor frecuencia de hemorragias y mejor preservación de la función articular.* **Conclusiones:** *La conciencia de enfermedad constituye un factor clave en la adherencia terapéutica en los pacientes con hemofilia. Las intervenciones dirigidas a fortalecer la autogestión del paciente podrían mejorar los resultados de salud a largo plazo.*

Palabras clave: *Hemofilia. Conocimiento. Adherencia al tratamiento.*

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Introduction

Hemophilia is a chronic genetic disorder characterized by a deficiency of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B), which predisposes affected individuals to spontaneous or post-traumatic bleeding episodes. Clinical classification is based on the level of coagulation factor activity and is divided into mild, moderate, and severe forms.[1] With therapeutic advances over recent decades, management has shifted from on-demand treatment of bleeding episodes to prophylactic strategies aimed at preventing hemorrhage and the consequent joint deterioration.[2] However, these therapeutic advances achieve their maximum effectiveness only when adequate patient adherence is present.

In this context, disease awareness has taken on a central role in the comprehensive management of hemophilia. This concept refers to the degree to which patients understand their diagnosis, the impact of the disease on daily life, and the need for continuous treatment.[3] Multiple studies have shown that greater disease awareness is associated with better adherence to prophylactic treatment, which in turn translates into fewer bleeding episodes, slower progression of hemophilic arthropathy, and improved quality of life.[1,4] Conversely, limited or distorted perception of the disease may lead to treatment discontinuation and the development of preventable complications.[5]

Systematic assessment of disease awareness and its relationship with therapeutic adherence has become a key line of research in hemophilia. Tools such as the Haemo-Adhaesion questionnaire have made it possible to study this relationship in different populations and contexts, showing consistent results:[6] patients with a better understanding of their condition present improved clinical and functional outcomes. In addition, evidence indicates that sustained educational interventions can reinforce treatment self-management, reduce the need for hospitalization, and promote a more active patient role in health care.[5]

Therapeutic adherence, however, is influenced by multiple factors. Among them, psychological and educational aspects are particularly relevant, especially in adolescents and young adults, who often underestimate the risks associated with the disease.[7] Structured educational programs tailored to different developmental stages have proven effective in this age group. Furthermore, socioeconomic factors such as access to health care centers, treatment costs, and resource availability directly affect treatment continuity. In this regard, health systems with inclusive and equitable policies achieve better adherence outcomes.[1,2]

Another determining factor is the family and social environment. Family support, interdisciplinary health care teams, and belonging to patient communities or support groups strengthen adherence and contribute to better quality of life.[8] The incorporation of technologies such as mobile applications and reminder systems, together with active patient participation in therapeutic decision-making, has also proven to be a promising strategy for improving adherence.

In light of these findings, the overall objective of the present study was to analyze the relationship between disease awareness and treatment adherence in patients with hemophilia, and its impact on clinical outcomes.

Methods

Study design

We conducted a longitudinal, prospective study with unstructured educational interventions over a 6-month period. The aim was to analyze the evolution of disease awareness and its relationship with therapeutic adherence and clinical outcomes in patients with hemophilia. The study was carried out within the framework of routine clinical practice; no additional visits were scheduled and no therapeutic changes were made. Educational interventions were limited to routine medical consultations and focused on communication and patient engagement. In adolescents and young adults, when lack of attention during the consultation was observed (e.g., mobile phone use), patients were directly addressed to encourage their involvement in understanding the disease and the therapeutic regimen. The study was approved by the institutional ethics committee, and all participants provided written informed consent.

Population and sample

The sample consisted of 2 groups:

- Patients older than 16 years with a diagnosis of hemophilia A who regularly attended clinical follow-up visits at the Hemophilia Foundation of Santa Fe (Rosario branch).
- Primary caregivers of patients younger than 16 years with hemophilia, also followed at the same institution.

Only patients or caregivers who provided informed consent and had complete clinical records at study entry were included.

Assessment instrument: disease awareness survey

A survey designed by the interdisciplinary team of the Hemophilia Foundation of Santa Fe was used to assess disease awareness. This instrument was developed based on prior evidence and validated at the institution, as no previously validated tool specifically assessing disease awareness in people with hemophilia was available. The survey consists of 15 items distributed across three main sections, exploring different dimensions of disease awareness:

- Section 1: knowledge of the disease. Includes questions on the genetic origin of hemophilia, the role of coagulation factors, differences between hemophilia A and B, and basic interpretation of common clinical tests.
- Section 2: self-care and treatment adherence. Assesses understanding of the prophylactic treatment regimen, frequency and regularity of administration, recognition of warning signs, and actions taken in bleeding situations.
- Section 3: perception of disease impact. Explores patient or caregiver perceptions regarding the physical, emotional, and social impact of hemophilia, including limitations in daily activities, adherence in school or work settings, and family coping.

Responses were recorded using 3- or 5-point Likert scales depending on the item. Partial scores and a total disease awareness score were calculated. The questionnaire was administered in paper format by trained personnel in a controlled clinical environment.

Procedure

Included patients and caregivers were evaluated at 2 time periods:

- Time 0: at study entry.
- 6 months: during a follow-up visit of the same participants assessed at time 0.

Notably, at the initial assessment, participants were not informed that they would be reassessed at 6 months, in order to minimize response bias and ensure spontaneity at the second evaluation.

At both visits, the following data were collected:

- Disease awareness survey.
- Annualized bleeding rate: number of bleeding episodes occurring over 6 months, extrapolated to an annual period.
- Progression of joint damage: assessed using the HEAD-US (Haemophilia Early Arthropathy Detection with Ultrasound) protocol.[9]
- Adherence to prophylactic treatment: determined according to the method proposed by Duncan et al.,[4] which includes actual treatment administration frequency relative to the prescribed regimen, as well as the occurrence of preventable events.

Statistical analysis

Categorical variables were compared between time points using McNemar's test, and continuous variables using paired Student's t test. The relationship between disease awareness and clinical variables was evaluated using Pearson's or Spearman's correlation coefficient, as appropriate. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using R software.

Results

A total of 48 participants were included: 30 male patients with hemophilia A (mean age, 19.3 years [range, 8-28]) and 18 caregivers (mean age, 42.1 years [range, 31-59]), of whom 72% were women and 28% men. All caregivers had a direct parental relationship (father, mother, or partner) and were affiliated with the Hemophilia Foundation of Santa Fe. Each patient was paired with their primary caregiver; therefore, no cases were duplicated.

Of the patients, 80% (n = 24) had severe hemophilia A and 20% (n = 6) had moderate hemophilia A with a severe bleeding phenotype (≥ 3-4 spontaneous hemarthroses per year, presence of ≥ 1 target joint, or repeated need for treatment for clinically relevant spontaneous bleeding). The same participants completed the survey at both time points: at study entry and at 6 months.

Section 1: Knowledge of the disease (Fig. 1)

At baseline, only 43.3% of patients (n = 13) correctly identified the type of hemophilia they had. This proportion increased significantly at 6 months, reaching 76.7% (n = 23) (p = 0.008). Similarly, 36.7% (n = 11) were aware of the severity of their diagnosis at baseline vs 73.3% (n = 22) at the 2nd assessment (p = 0.012).

A critical issue was lack of knowledge regarding treatment: 56.7% of patients (n = 17) were unable to

name either the type or the commercial name of their coagulation factor at baseline. This proportion decreased to 26.7% (n = 8) at 6 months (p = 0.015).

Among caregivers, overall knowledge of the disease also improved. At baseline, 77.8% (n = 14) correctly identified the basic mechanisms of coagulation, increasing to 94.4% (n = 17) at 6 months (p = 0.021).

Notably, in the group of adolescents and young adults (16-24 years), only 25% correctly identified the mode of inheritance of hemophilia at baseline; this percentage increased to 56% at 6 months (p < 0.05).

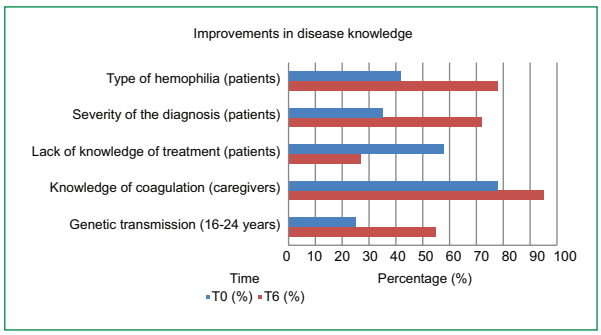

Figure 1. Changes in disease knowledge between the baseline visit and the 6-month follow-up.

Section 2: Self-care and treatment adherence

At baseline, only 40% of patients (n = 12) reported strict adherence to the prescribed prophylactic regimen. At 6 months, this proportion increased significantly to 73.3% (n = 22) (p = 0.004). Improved adherence was associated with a significant reduction in the annualized bleeding rate: median of 5.2 events per year at baseline vs 1.9 events per year at 6 months (p = 0.003).

Among caregivers, 83.3% (n = 15) reported feeling confident administering treatment in the absence of health care personnel at baseline; this proportion increased to 94.4% (n = 17) at 6 months (p = 0.031).

Of note, in the 16-24-year age group, low initial engagement in self-care was observed, reflected by limited attention during consultations (eg, mobile phone use when receiving instructions). However, this pattern showed slight improvement following the educational intervention.

Section 3: Perception of disease impact

Perception of the disease improved in both groups. At baseline, 46.7% of patients (n = 14) perceived hemophilia as a major limitation in daily life, whereas at 6 months this proportion dropped down to 20% (n = 6) (p = 0.009). In parallel, the proportion of patients who stated that they "can lead a normal life if they take proper care" increased from 50% (n = 15) to 83.3% (n = 25) (p = 0.002).

Among caregivers (n = 18), initial perception of hemophilia as a major limitation was higher, at 61.1% (n = 11), but decreased to 27.8% (n = 5) at 6 months (p = 0.01). Likewise, the proportion of caregivers who believed that "a normal life is possible with appropriate care" increased from 44.4% (n = 8) to 77.8% (n = 14) (p = 0.005).

Concern regarding the possibility of spontaneous bleeding decreased significantly in both groups. Among patients, 66.7% (n = 20) reported high concern at baseline, decreasing to 36.7% (n = 11) at 6 months (p = 0.01). Among caregivers, concern was initially higher, with 83.3% (n = 15) reporting high concern, decreasing to 50% (n = 9) at follow-up (p = 0.02).

Perceived self-efficacy in disease management increased significantly. Among patients, the proportion who felt capable of managing their condition increased from 40% (n = 12) to 76.7% (n = 23) (p = 0.004). This change was particularly marked in adolescents (n = 12), in whom perceived self-efficacy increased from 25% (n = 3) to 66.7% (n = 8) (p = 0.03). Among caregivers, self-efficacy increased from 55.6% (n = 10) to 88.9% (n = 16) (p = 0.008).

Notably, 100% of participants (patients and caregivers) expressed interest in receiving additional information and education about hemophilia at the end of the study, underscoring the importance of systematic educational interventions (Table 1).

In the subgroup of patients on emicizumab, a specific pattern of therapeutic adherence was identified. During episodes of joint pain or other hemophilia-related symptoms, adherence increased significantly. However, this improvement was transient: once acute symptoms resolved and perceived threat diminished, adherence tended to progressively decline. This pattern was observed even in patients with adequate plasma drug concentrations and no inhibitors.

Discussion

Disease awareness in individuals with hemophilia A represents a critical and dynamic dimension that directly influences treatment adherence and, consequently,

Table 1. Changes in knowledge, self-care, and disease perception between baseline and 6-month visits

Variable	Baseline	6 months	p
Patients, n (%)			
Knowledge of type of hemophilia	13 (43.3%)	23 (76.7%)	0.004
Knowledge of disease severity	11 (36.7%)	22 (73.3%)	0.006
Does not know medication (name or factor type)	17 (56.7%)	8 (26.7%)	0.018
Strict adherence to prophylaxis regimen	12 (40.0%)	22 (73.3%)	0.011
Perceives hemophilia as a major limitation	14 (46.7%)	6 (20.0%)	0.022
Believes a normal life is possible with proper care	15 (50.0%)	25 (83.3%)	0.003
Adolescents recognizing mode of transmission (16-24 years)	4/16 (25.0%)	9/16 (56.0%)	0.049
Caregivers, n (%)			
Knowledge of basic coagulation mechanisms	14 (77.8%)	17 (94.4%)	0.157
Feels confident administering treatment without health care staff	15 (83.3%)	17 (94.4%)	0.317
Both groups, n (%)			
Desire further education on hemophilia at study completion	48 (100%)	48 (100%)	-

clinical outcomes. Our findings confirm what has been previously reported in the literature: greater understanding of the disease is associated with improved adherence, a lower frequency of bleeding events, and a more positive perception of quality of life.[10]

The behavior observed in patients receiving emicizumab highlights an emerging clinical paradox. Despite the high efficacy and convenience of treatment, adherence tends to decline as symptoms are mitigated and the disease becomes less perceptible. This underscores that, even in scenarios of optimal clinical control, disease awareness remains an essential component of management. The absence of symptoms should not be equated with the absence of disease, and commitment to treatment must be sustained beyond overt physical discomfort.

The improvement observed in knowledge regarding hemophilia severity, type of treatment, and perceived self-efficacy following simple, systematic educational interventions indicates that these strategies have a tangible clinical impact. In particular, the adolescent subgroup, which started from a lower baseline level of knowledge, showed significant gains, although it continues to represent a challenge because of lower initial engagement in self-care. The transition from adolescence to adulthood remains a critical period that requires personalized, sustained, and patient-centered interventions.

At our center, educational strategies have been implemented to empower both patients and caregivers. In adolescents, active participation in clinical consultations is strongly encouraged, aiming to shift the exclusive focus from the responsible adult toward direct dialogue with the young patient. Practices such as extended consultation time, clear and age-appropriate therapeutic explanations, and encouragement to listen and actively participate during medical visits have been incorporated. These low-cost actions seek to build autonomous and sustained disease awareness.

In this context, the concept of a "hemophilia-free mind," proposed by Krumb and Hermans,[11] is appealing as an intervention goal, although it should be interpreted with caution. Far from implying disengagement, this concept refers to a healthy integration of the diagnosis, in which the disease does not define the patient's identity or limit aspirations. Achieving this state requires not only therapeutic efficacy but also continuous education and strengthening of the patient-health care team relationship.[11]

Nevertheless, structural barriers persist. Inequalities in access to prophylaxis and diagnostic technologies, such as musculoskeletal ultrasound, hinder early detection of joint complications and limit the impact of educational interventions, particularly in resource-limited settings.[2] In this regard, it is essential to develop educational materials and strategies tailored to the sociocultural realities of each community, integrating biomedical information with psychosocial and family aspects.

Similarly, the role of caregivers as active agents in treatment is particularly relevant. Their involvement and training emerge as pillars for sustaining long-term adherence, especially in environments where access to the health care system is intermittent or insufficient. Shared construction of knowledge, trust, and therapeutic commitment helps to partially overcome these structural limitations.

Finally, the systematic incorporation of tools to assess disease awareness into routine clinical practice could facilitate early identification of patients at risk for poor

adherence. This would allow more efficient allocation of resources and the development of more personalized educational programs, including longitudinal follow-up, accessible digital supports, and approaches centered on the individual and their environment.

Conclusions

The findings of this study reinforce the clinical value of promoting disease awareness in hemophilia A as an effective strategy to improve treatment adherence and reduce complications. Simple educational interventions, implemented systematically, were shown to generate sustained improvements in patient knowledge, perceived self-efficacy, and ownership of care.

Disease awareness should not be considered solely an educational objective but also an essential component of comprehensive clinical management. Future studies should aim to expand the sample size and further analyze specific subgroups to optimize educational interventions according to age, baseline level of knowledge, and sociocultural context.

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Conflicts of interest

None declared.

Ethical considerations

Protection of persons and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible human experimentation committee and with the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The recommendations of the SAGER guidelines were followed, according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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ORIGINAL RESEARCH ARTICLE

Indirect comparison of gene therapies in hemophilia A with use of generative artificial intelligence

Comparación indirecta de terapias génicas en la hemofilia A con uso de inteligencia artificial generativa

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Abstract

Introduction: *Gene therapy revolutionises treatment in haemophilia A, with promising results, but different safety and efficacy profiles.* **Objective:** *To indirectly compare efficacy and safety of valoctocogene roxaparvovec (VR) and giroctocogene fitel-parvovec (GF).* **Material and method:** *Published data of VR and GF were analysed. Statistical tests proposed by ChatGPT-4o were used for comparisons.* **Results:** *FVIII levels > 5%, no significant differences at 24 months (p = 0.516). For total annualized bleeding rate, similar reductions without statistical significance (p = 0.263). GF showed less need for corticosteroids (p = 0.0012). 81.3% of RV patients had no bleeding, significantly higher than 64% of GF (p = 0.014).* **Conclusions:** *Both therapies are effective, with limitations. GF stands out for lower corticosteroid use and FVIII stability. RV has better control of spontaneous bleeding. These differences reflect challenges in clinical study design and comparison, and further evaluation is needed.*

Keywords: *Gene therapy. Hemophilia A. Valoctocogene. Roxaparvovec. Giroctocogene. Fitelparvovec.*

Resumen

Introducción: *La terapia génica está revolucionando el tratamiento de la hemofilia A, con resultados prometedores, pero distintos perfiles de seguridad y eficacia.* **Objetivo:** *Comparar indirectamente la eficacia y la seguridad de valoctocogén roxaparvovec (VR) y giroctocogén fitelparvovec (GF).* **Material y método:** *Se analizaron los datos publicados de VR y GF. Para las comparaciones se usaron pruebas estadísticas propuestas por ChatGPT-4o.* **Resultados:** *En cuanto a niveles de factor VIII > 5%, no hay diferencias significativas a 24 meses (p = 0.516). En la tasa anualizada de sangrado total se produ-cen reduc-ciones similares, sin significancia estadística (p = 0.263). El GF mostró menor necesidad de corticosteroides (p = 0.0012) El 81,3% de los pacientes con VR no presentaron sangrados, significativamente superior al 64% de los tratados con GF (p = 0.014).* **Conclusiones:** *Ambas terapias son eficaces, pero con limitaciones. El GF destaca por el menor uso de corti-costeroides y la estabilidad del factor VIII. El VR logra un mejor control de los sangrados espontáneos. Estas diferencias reflejan desafíos en el diseño y la comparación de estudios clínicos, y se requieren evaluaciones adicionales.*

Palabras clave: *Terapia génica. Hemofilia A. Valoctocogen. Roxaparvovec. Giroctogene. Fitelparvovec.*

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Introduction

Hemophilia A is caused by mutations in the *F8* gene, which provides instructions for producing factor VIII (F8), a protein required for normal blood coagulation. In the absence of functional F8, blood cannot clot properly, leading to prolonged bleeding episodes.[1,2] The monogenic nature of hemophilia, both A and B,[1] makes it an ideal disease for exploring gene therapy approaches. Gene therapy using liver-directed adeno-associated viruses (AAVs) offers the possibility of a functional – though not definitive – cure for this condition.[3,4] To date, one AAV serotype 5–based gene therapy has been approved for use in hemophilia A: valoctocogene roxaparvovec (VR) (Roctavian®, BioMarin Lab),[5] which is available in some countries worldwide. The results of the phase III clinical trial including 134 participants who received a single infusion of an AAV5 vector and completed > 51 weeks of follow-up were published in 2022.[6] Among the 132 participants who were negative for human immunodeficiency virus, mean F8 activity levels increased by 41.9% at weeks 49 to 52. In the 112 rollover participants, the mean annualized rates of F8 concentrate use and treated bleeding after week 4 decreased by 98.6% and 83.8%, respectively, following infusion. All participants experienced at least one adverse event, although only 22 (16.4%) were classified as serious. Alanine aminotransferase (ALT) elevations were reported in 85.8% of participants, and 79.7% received corticosteroid therapy. No inhibitors against F8 were reported.

At the most recent American Society of Hematology Congress held in San Diego (CA, United States, December 2024), promising results were presented from the phase III AFFINE clinical trial evaluating giroctocogene fitelparvovec (GF), a novel gene therapy based on an AAV serotype 6 vector targeting hepatocytes.[7] This vector encodes a B-domain–deleted variant of human F8 and, following administration of a single dose, is intended to induce sustained endogenous F8 synthesis in individuals with hemophilia A. In the study, 75 participants received GF, with a median follow-up duration of 16.8 months (range, 7.8-44.4). Of these, 50 were included in the efficacy population, with a median follow-up of 33.6 months (range, 14.5-44.4). A statistically significant reduction in mean annualized total bleeding rate was observed (from 4.73 to 1.24) from week 12 through ≥ 15 months after infusion vs prior prophylaxis. At month 15, 84% of participants had F8 activity levels > 5%, and 82.2% (n = 29) maintained these levels at year 2. The annualized treated bleeding rate dropped from 4.08 down to 0.07 between week 12 and ≥ 15 months after infusion. A total of 64% of participants experienced no bleeding events, and 88% had no treated bleeding events. F8 consumption dropped by 99.8%, and only 1.3% of participants resumed prophylaxis at a median of 16.1 months after infusion. A total of 624 adverse events were reported in 98.7% of participants, of which only 26 were serious; pyrexia was the most common (54.7%). ALT elevation was observed in 46.7% of participants, and 38.7% reported headache. Corticosteroids were administered to 62.7% of participants for ALT elevation or declining F8 levels, with a mean total treatment duration of 114.6 days (range, 11-296). Transient F8 levels > 150% (chromogenic assay) were reached by 49.3% of recipients, and 30.7% (n = 23) received prophylactic anticoagulation. Based on these results, Sangamo Therapeutics intends to seek regulatory approval for this new gene therapy from United States authorities.

In parallel, the potential of ChatGPT as a decision-support tool for health care professionals – specifically in the field of hemophilia – has been increasingly recognized.[8] Indeed, freely available applications already exist (https://codigorojo.tech/home/) for hematologists and other specialists. In the absence of adjusted indirect comparisons between these gene therapies, generative artificial intelligence offers the possibility of performing an indirect comparison between them.

The objective of this study was to indirectly compare the approved gene therapy for hemophilia A (VR) with the new gene therapy pending approval (GF).

Methods

VR and GF were compared using the results of the phase III clinical trials reported by Ozelo et al.[6] for VR and by Leavitt et al.[7] for GF. Statistical significance analyses were performed according to the tests proposed by ChatGPT-4o. The variables analyzed included plasma F8 levels at 12 and 24 months; mean annualized total bleeding rate and percentage reduction of patients with 0 spontaneous bleeds; reduction in F8 concentrate consumption; common adverse effects; ALT elevation and corticosteroid use; resumption of F8 prophylaxis; and use of prophylactic anticoagulation (Table 1). In addition, the percentage decline in F8 levels over time was analyzed.

Table 1. Phase III clinical trial results

Parameters	Giroctocogene fitelparvovec (n = 75)	Valoctocogene roxaparvovec (n = 134)
F8:C (12/24 months)	84% > 5%*/82.8% > 5%	88.1% > 5%/77% > 5%
Total ABR/reduction in treated spontaneous bleeding	1.24/73.76%	0.8/81.3%
Reduction in F8 consumption	99.8%	98.6%
Common adverse events	Fever (54.7%), ALT elevation (46.7%)	ALT elevation (85.8%), headache (38.1%)
Corticosteroid use/Treatment duration (mean)/ Adverse effects	62.7%/114.6 days (range: 11-296)/25.3%	79%/234.5 days (range: 22-551)/72%
Resumption of prophylaxis	1.3%	0%
Prophylactic anticoagulation	30.7% (due to F8 ≥ 150%)	0%

*Month 15.
ALT: alanine aminotransferase; F8:C: factor VIII coagulant assay; ABR: annualized bleeding rate.

Results

Table 1 illustrates the variables compared. The publication by Ozelo et al.[6] was selected due to its follow-up duration, which is comparable to that of the AFFINE trial.[7] ChatGPT-4o considers both therapies effective but identifies notable differences, some of which reach statistical significance, applying different statistical tests accordingly. When comparing proportions, the chi-square test was used, and when sample sizes were small, Fisher exact test was applied. For comparisons of means or percentage reductions, independent t tests were used for normally distributed data and Mann–Whitney U tests otherwise. For example, in comparing the proportion of patients receiving prophylactic anticoagulation – given the very low proportions or rare events (1.3% for GF and 0% for VR – the Fisher exact test was considered more appropriate than the chi-square test. When comparing mean corticosteroid treatment duration, independent *t* tests were applied using estimated means, standard deviations (based on range), and sample sizes. For larger independent groups, Z tests for proportions were used when assumptions were met, although chi-square testing would have been equally appropriate. No statistically significant difference was observed between therapies in the proportion of patients with plasma F8 levels > 5% at 24 months (p = 0.516, chi-square test), nor in the proportion of patients resuming prophylaxis (p = 1.0, Fisher's exact test), nor in the reduction of annualized bleeding rate (p = 0.263, Z statistic). In contrast, ALT elevation differed significantly in favor of GF (p = 0.0012, chi-square test), although a high proportion of patients on GF required prophylactic anticoagulation (30.7%). This ALT elevation may explain the statistically significant difference in corticosteroid use, which was higher among VR recipients (p = 0.0075, Z statistic), even after adjustment for the larger sample size in the VR group, as well as the longer duration of corticosteroid therapy (mean, 234.5 days vs 114.6 days; $p = 6.93 \times 10^{-12}$, independent *t* test, favoring GF) and the higher rate of adverse effects (72% vs 25.3%; $p = 7.38 \times 10^{-11}$, Z test for proportions, favoring GF). No statistically significant difference was found in the reduction of the percentage of patients with 0 treated spontaneous bleeds (p = 0.193, Z statistic), although a significant difference was observed in the percentage of patients with 0 spontaneous bleeds overall (p = 0.0055, Z statistic). Finally, a test comparing the difference in proportions between 2 independent groups was applied to assess the decline in patients with F8:C levels > 5%. For GF, the p value for decline was 0.872 (the 1.2% decrease in F8:C levels between months 15 and 24 was not statistically significant). For VR, the p value was 0.018 (the 11.1% decrease between months 12 and 24 was statistically significant). The comparison between therapies yielded a p value of 0.114, not reaching statistical significance.

Overall, GF appeared to stand out for the stability of F8 levels – at least during this early phase – and for a more favorable safety profile, with statistically significant lower ALT elevation, reduced need for corticosteroids, shorter treatment duration, and fewer corticosteroid-related adverse effects. VR's main strengths appeared to be greater reductions in treated spontaneous bleeding and a higher proportion of patients free from these events.

Table 2. Strengths and weaknesses of gene therapies for hemophilia A

Item	Giroctocogene fitelparvovec	Valoctocogene roxaparvovec
Factor VIII stability	+++	++
Corticosteroid use	++	+
Corticosteroid-related adverse effects	++	+
Reduction in spontaneous bleeding	++	+++

Conclusions

Gene therapies for hemophilia A, although promising, remain far from optimal, particularly when compared with gene therapy for hemophilia B. The 2 available gene therapies for hemophilia A, each with distinct advantages and limitations (Table 2), face well-known constraints. GF appears to provide more sustained F8 expression – at least within the first 2 years after infusion – with a smaller percentage decline over time. Additionally, lower ALT elevation and reduced corticosteroid use (and duration) suggest potentially lower immunogenicity associated with AAV serotype 6. Nevertheless, longer-term follow-up and direct comparative analyses are required to confirm these advantages. In fact, ChatGPT-4o highlights the inherent difficulty of comparing 2 studies with different designs and populations; however, the analysis yields informative insights into the relative performance of each treatment. Although this was an unadjusted statistical evaluation rather than an adjusted indirect comparison, we believe it provides valuable preliminary information that may assist in selecting one gene therapy over another, should GF receive regulatory approval, beginning with the U.S. Food and Drug Administration. It must be emphasized that ChatGPT-4o is not validated for this type of analysis, and further studies are required to legitimize its use, particularly regarding statistical test selection; nonetheless, it may represent an accessible and potentially useful tool for such evaluations.

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments were conducted on humans or animals for this research.

Confidentiality, informed consent, and ethical approval. The authors followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The recommendations of the SAGER guidelines were followed, according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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REVIEW ARTICLE

Prophylaxis in hemophilia A: beyond PK – the potential role of procoagulant platelet in the hemostatic activity of rFVIIIa

Profilaxis en hemofilia A: más allá de la PK – el papel potencial de las plaquetas procoagulantes en la actividad hemostática del rFVIIIa

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Abstract

Hemophilia A (HA), a hereditary bleeding disorder arising from mutations in the clotting factor VIII (FVIII) gene, disrupts the intrinsic blood coagulation pathway. Treatment primarily aims to prevent bleeding episodes by replenishing deficient clotting factor levels through intravenous clotting factor concentrate infusion. The advent of replacement therapy using FVIII concentrates has significantly advanced treatment, enhancing protection against bleeds and reducing arthropathy. This narrative review seeks to provide an overview of the importance of eradicating bleeds and the therapeutic potential of recombinant FVIII (rFVIII)-based replacement therapy. We explored the available evidence on the hemostatic mechanisms triggered by rFVIII in prophylaxis and the role of phospholipid membranes of activated platelets in FVIII-mediated FX-activation and thrombin burst. Key insights from the congresses of the International Society on Thrombosis and Hemostasis (2022) and the European Association for Hemophilia and Allied Disorders (2023) are also discussed. This review discusses the importance of optimizing prophylactic FVIII regimens through personalized approaches considering each patient's bleeding profile, clinical conditions, and lifestyle preferences for achieving joint health and quality of life. We also explored the potential role of rFVIII affinity for procoagulant platelets in hemostasis among HA patients.

Keywords: *Hemophilia A. Prophylaxis. FVIII. Joint damage. Platelets. Hemostasis.*

Resumen

La hemofilia A, un trastorno hemorrágico hereditario causado por mutaciones en el gen del factor de coagulación VIII (FVIII), afecta a la vía intrínseca de coagulación sanguínea. El objetivo terapéutico principal es prevenir los episodios hemorrágicos restableciendo los niveles deficientes de factor de coagulación mediante infusiones intravenosas de concentrados de ese factor. La terapia de reemplazo con concentrados de FVIII ha revolucionado el tratamiento, mejorando la protección contra sangrados y reduciendo la artropatía. En esta revisión narrativa se ofrece una visión general sobre la importancia de erradicar sangrados y el potencial de la terapia de reemplazo con FVIII recombinante (rFVIII), y se explora la evidencia disponible sobre los mecanismos hemostáticos desencadenados en profilaxis por el rFVIII y las membranas de fosfolípidos de las plaquetas procoagulantes en la explosión de trombina mediada por la activación de FX. También se discuten los hallazgos más relevantes presentados en los congresos ISTH 2022 y EAHAD 2023. Igualmente se aborda la importancia de

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personalizar los regímenes profilácticos de FVIII según el perfil hemorrágico, condiciones clínicas y preferencias de estilo de vida de cada paciente para lograr una buena salud articular y calidad de vida.

Palabras clave: *Hemofilia A. Profilaxis. FVIII. Daño articular. Plaquetas. Hemostasis.*

Introduction

Hemophilia A (HA) is an X-linked recessive disorder caused by a deficiency of clotting factor VIII (FVIII), the coding gene of which is located on the long arm of the X chromosome (Xq28). Most cases are due to single nucleotide variants, although other types of genetic alterations can also cause the disease.[1] The clinical severity of hemophilia is established according to baseline plasma FVIII levels, and the risk of bleeding is classified into three risk or severity levels, defined as mild, moderate, or severe (Table 1).[2]

Prophylaxis is the standard of care for patients with severe forms of HA whose plasma FVIII levels are below 1% (FVIII: C < 1%). The aim is to prevent bleeding, especially joint bleeding, and its consequences, for example, hemophilic arthropathy.[2] Only patients with severe HA with FVIII: C < 1% were traditionally considered candidates for prophylaxis, since it was believed that patients with moderate HA and FVIII: C levels between 1% and 5% presented few bleeds. Prophylaxis was therefore based on a target procoagulant factor trough levels of 1%, and the objective was to convert severe HA into moderate HA.[3] This approach raises two questions: (1) Should prophylaxis be restricted to severe HA patients? and (2) does setting target trough levels of 1% offer sufficient protection against bleeding? Or in other words, how much bleeding is too much?

Prophylaxis

Which patients should receive prophylaxis?

Patients with severe HA who have frequent spontaneous bleeds are obvious candidates for prophylactic treatment. The benefits of prophylaxis in these patients have been known for years, as Manco-Johnson et al. observed in children with severe HA in 2007.[4] The ESPRIT study in particular confirmed the efficacy of prophylaxis in preventing bleeding and arthropathy in this population, especially in the case of early-onset hemophilia.[5]

Most prospective clinical trials of HA prophylaxis are restricted to severe HA, and patients with non-severe HA, a population in whom spontaneous bleeding is occasional but who may also present prolonged bleeding following trauma or minor surgery, are excluded. Although bleeding frequency may be considered tolerable by patients with non-severe HA, it may have mid- to long-term consequences, and as in severe HA patients, the impact on joint damage deserves special attention since “the severity of joint deterioration is the main factor affecting morbidity and quality of life (QoL)”.[6]

Nevertheless, non-severe HA is given less attention, and this is probably why patients themselves tend to lose sight of the severity of their condition. A recent study by Walsh et al.[7] found that the different unmet needs in patients with non-severe HA were related to their disregard of the importance of their disease, their reduced contact with the rest of the patient community (i.e., through patient associations), their frequent lack of engagement with hospital visits, and the absence of specific health indicators for this population. In clinical terms, two or three bleeds occurring in the same joint can cause progressive and irreversible damage.[8] Since hemophilia is a chronic inherited disease, it makes sense to think that sooner or later, depending on the patient’s phenotype, patients with non-severe HA may also develop hemophilic arthropathy.

Patients with severe HA receiving prophylaxis have better musculoskeletal outcomes than patients with moderate HA who are treated on demand. The PROBE study, which included a subgroup of 134 patients with moderate HA, showed that only 35% received continuous prophylaxis, although 82% reported more than 2 or 3 bleeds in the 12 months before treatment.[9] These bleeds caused joint damage, to the extent that 74.42% of the patients had joints with a compromised range of motion and 70% needed some type of mobility aid. Furthermore, 77.3% of patients with moderate HA reported acute pain and 71.4% suffered chronic pain, and only 12.8% did not need analgesia to achieve pain control. These data were associated with a considerable impact on QoL, as 61.6% of patients reported difficulties in coping with activities of daily living. This evidence confirms that most patients with moderate HA and also those with mild HA are not offered protection against joint damage, to the detriment of their QoL.

Table 1. Clinical severity of hemophilia A according to clotting FVIII levels and bleeding severity

Severity	Severe	Moderate	Mild
Clotting factor level	< 1 IU/dL or < 1% of normal	1-5 IU/dL or 1-5% of normal	5-40 IU/dL or 5- < 40% of normal
Bleeding	Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery	Severe bleeding with major trauma or surgery; rare spontaneous bleeding

FVIII: factor VIII; IU: international units.
Adapted from Srivastava et al.[2]

The conclusions of the MoHem study are consistent with these findings and revealed an association with patient age.[10] This study evaluated the prevalence of arthropathy in a group of patients with moderate HA and hemophilia B. Of the 145 patients evaluated (median age 28 years), 61% had HA and a median FVIII of 3%, and 85% of patients had a history of hemarthrosis. The study highlighted the prevalence of severe arthropathy in the subgroup of patients with baseline FVIII: C levels ≤ 3%. Moreover, when these patients were compared with another cohort of patients with severe HA receiving prophylaxis, it was observed that patients with moderate HA achieved a value of > 10 in the Hemophilia Joint Health Score in half the time. The study authors found that the time between the age at which the first bleed occurred (a median age of 5 years) and the age at the start of prophylaxis (a median age of 10 years) was key in the development of joint deterioration, and primary prophylaxis was recommended for all patients with FVIII: C trough levels of ≤ 3%.

Álvarez Román et al. evaluated arthropathy in six typical target joints (ankles, knees, elbows) in 28 adult patients with HA (mean age 42.5 years), of whom 14 had moderate HA and 14 had mild HA. Of the total number of patients, 22 received on-demand treatment.[11] Tests included assessment of arthropathy using the Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) scoring system. A HEAD-US value of 0 was recorded for all joints in five of the patients with mild HA (37.5%) and in 3 of the patients with moderate HA (21.4%). In eight patients, damage was observed in at least one target joint, suggesting a delay in the detection of damage and, as such, suboptimal prevention of possible joint damage in these patients. Based on the HEAD-US score obtained, the authors decided to switch the treatment modality to prophylaxis in 25% of patients with mild HA and 33% of patients with moderate HA. The study concluded that arthropathies could also be detected in patients with both mild and moderate HA. Therefore, in the non-severe HA scenario, it is equally important to offer appropriate joint damage prevention. The authors stressed the importance of close monitoring during patient visits and periodic ultrasound reviews of the 6 target joints as a guide to designing a treatment strategy.

All the accumulated evidence has prompted the World Federation of Hemophilia to emphasize in their consensus guidelines for the treatment of hemophilia (recommendation 6.1.1) that prophylaxis should be offered to patients with a severe bleeding phenotype and that patients with moderate HA should be considered equally in this regard.[2] Similarly, but more specifically, the UK Hemophilia Centre Doctors' Organization guidelines[12] recommend prophylaxis for all children with baseline FVIII levels of 1-3%; for any hemophilia patient with ≥ 1 spontaneous hemarthroses; and for anyone with established joint damage due to hemarthroses who experience continuous bleeding.

What should be the aim of prophylaxis?

The conventional target population for prophylaxis was patients with severe HA, and the aim was to maintain a minimum FVIII level of > 1% before the following infusion, and thus to convert their severe HA to moderate HA. But was this really achieved? Not really. We know that regular infusion of FVIII produces a "peak/trough" effect. Following intravenous infusion of FVIII, there is a rapid increase in plasma FVIII levels that may reach normal or near normal levels. In the following hours, depending on the concentrate used and the patient's metabolism, FVIII levels fall.[13,14] When FVIII levels fall to 1% (in approximately 48-72 h), the next infusion is administered. Thus, between infusions, the patient with severe HA receiving FVIII prophylaxis will rapidly achieve plasma FVIII levels similar to those of

a healthy individual (FVIII: C > 40%), and in the hours before the next infusion, their levels will be those of a patient with moderate HA (FVII: C > 1% and < 5%). Even so, most of the time between infusions, FVIII levels will correspond to those of an individual with mild HA (FVII: C > 5% and < 40%). For this reason, Collins et al. argue that it is important not to confuse baseline FVIII levels of 2% (which may occur in a patient with moderate HA treated on demand) with target trough levels of 2% in a patient with severe HA receiving prophylaxis, since this patient will always be more protected against bleeding due to the peak or elevation of FVIII and the larger FVIII area under the curve (Fig. 1).[15]

However, in a scenario of better joint health and improved QoL in HA patients, target trough values of 1% are becoming obsolete. Several studies support higher target trough values in individuals receiving FVIII prophylaxis. The latest WHF guidelines (in recommendation 6.3.1) point out that although minimum levels of 1 IU/dL (1%) were previously considered optimal, they do not reduce the risk of bleeding, so currently most doctors prefer to aspire to a higher target trough concentrations (from > 3% to ≥ 5%) that, according to recent studies, effectively reduce the risk of bleeding.[2] Chowdary et al. reported that for FVIII trough levels of between 1% and 10%, each 1% increase was associated with 2% more patients without bleeding.[16]

At this point, we should emphasize that although aiming at target trough levels is a good starting point, the main objective of prophylaxis should be to achieve zero bleeds and to offer patients with HA QoL similar to that of the general population. It is vitally important to adapt prophylaxis to the individual bleeding pattern of each patient, which often overrides considerations such as minimum FVIII levels.[15]

Recombinant FVIII prophylaxis: beyond pharmacokinetics (PKs)

Extended half-life (EHL) recombinant FVIII factors (rFVIII) have been designed to provide patients with longer-lasting therapy than offered by standard half-life (SHL) rFVIII. The technology used to generate these new factors allows patients receiving prophylaxis to reduce the frequency of infusion and/or the dose. These EHL-rFVIII can maintain higher minimum FVIII levels and are recommended by international clinical guidelines.[2]

Most clinical trials of personalized prophylaxis in severe HA conducted in recent years have prioritized treatment optimization in terms of dosing intervals and factor use over protection against bleeding. In a recent systematic review, Di Minno et al. indirectly compared several clinical trials of personalized prophylaxis with different EHL-rFVIIIs and one of the most commonly used SHL-rFVIII (octocog alfa or Advate®) after 6 months. The authors concluded that while all of the EHL-rFVIII concentrates had improved the dosing interval and consumption, the median annualized bleeding rate did not improve, and even worsened for most of them (Fig. 2).[17]

The first prospective clinical trial of PK-guided personalized prophylaxis targeting FVIII trough levels higher than 1-3% was published in 2021. This was a study with a 6-month observation period in which an EHL-rFVIII was used to take advantage of its lower plasma clearance and thus maintain higher FVIII trough levels than usually recommended.[18] Patients were treated with rurioctocog alfa pegol, a third-generation rFVIII obtained from murine cell line cultures and chemically modified by the addition of a polyethylene glycol group. Patients were randomized to two arms in which different FVIII target trough levels were set (1-3% or 8-12%) to determine whether higher trough levels offered better bleeding protection. Higher target trough levels were seen to improve both the annual bleeding rate (ABR) (1.6 *versus* 3.6, respectively) and the proportion of patients with zero bleeds (62% *versus* 42%, respectively), while the number of weekly infusions (3-4 *versus* 2, respectively) and factor consumption (143.6 IU/kg *versus* 66.2 IU/kg, respectively) increased. These results underline the need for personalized treatment (Table 2).

But are EHL-rFVIII concentrates the best treatment option for mild and moderate HA? FVIII is considered to have an EHL only because of the technology used to prolong its plasma half-life (T1/2) and PK criteria, but clinical criteria are not taken into account. Other factors may also affect the effectiveness of the product, such as the source cell line, post-translational modifications, or chemical modifications. Platelets are the cells most intrinsically associated with the coagulation process, as they provide the surface on which most of the thrombin necessary for clot formation is produced. For the thrombin burst to occur, the activated platelets must interact with FVIII. This happens when platelets previously activated by thrombin enter a “procoagulant” state and express phosphatidylserine, which facilitates the binding of FVIII to the platelet surface.[19] *In vitro* experiments

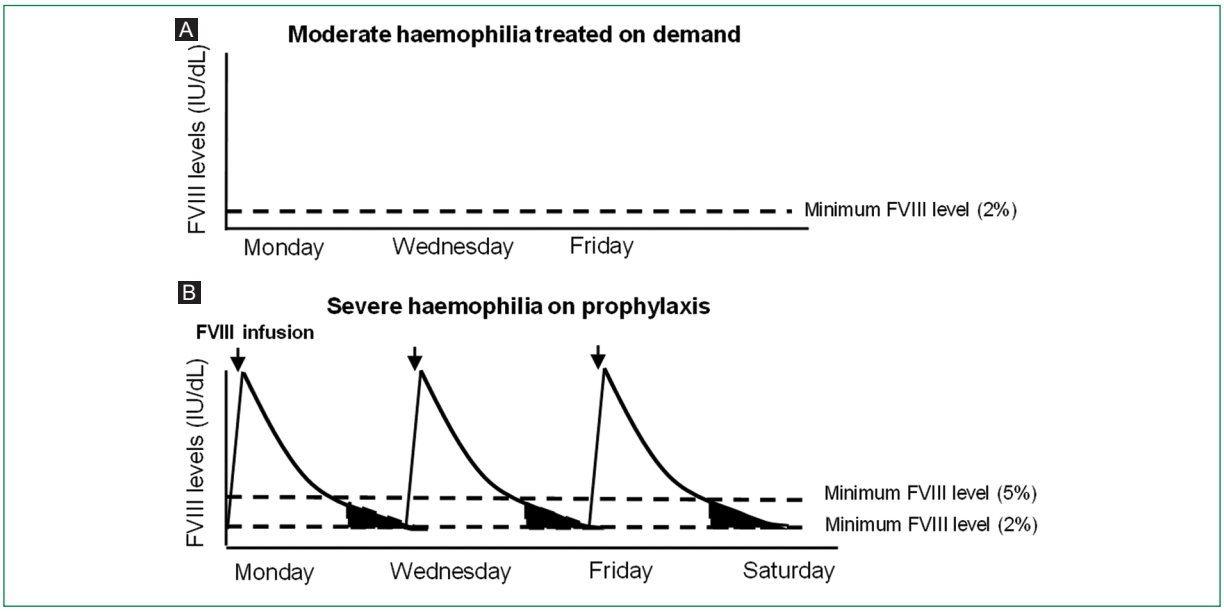

Figure 1. Schematic representation of the time spent at different clotting factor levels comparing **A:** moderate hemophilia treated episodically. In moderate hemophilia, the baseline level of factor VIII (FVIII) is consistently low throughout the week with no peaks of FVIII/FIX at the time of potential trauma or physical activity. In this scenario, factor infusion will not provide any additional benefit and **B:** severe hemophilia on prophylaxis with trough level at 2 IU/dL. In severe hemophilia patients on prophylaxis, higher levels of the factor are detected at all time points, which most of the time are within a mild range level. These patients can adapt factor infusions to ensure normal FVIII levels at the time of predictable hemostatic challenges *(adapted from Collins et al.[15]).*

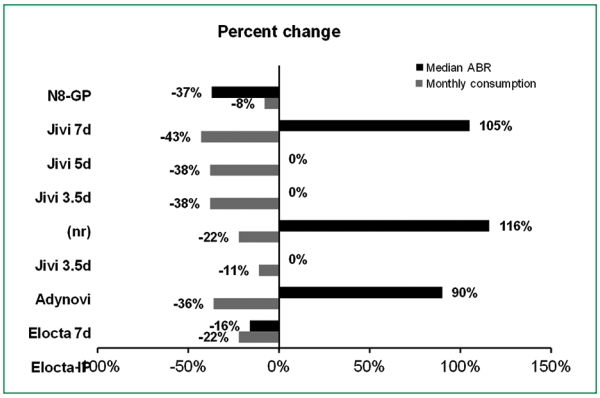

Figure 2. Percentage changes in monthly concentrate consumption and ABR for several EHF factor VIII concentrates as compared with octocog alfa (Advate®) in a PK-guided prophylaxis regimen. ABR: annualized bleeding rate; d: days; IP: individualized prophylaxis; nr: patients receiving BAY-94 9027 with ≤ 1 bleeding episode before randomization, eligible for randomization but treated twice weekly *(adapted from Di Minno et al.).*[17]

have shown that, while the activated factors FVIIIa and FIXa can form a tenase complex in solution in plasma, FIXa has 10 times more affinity for FVIIIa when FVIIIa is bound to a phospholipid surface similar to that of the activated platelet membrane. However, it has a greater effect on the catalytic activity of the tenase complex FVIIIa-FIXa, which in the presence of these membranes is capable of generating 1,500 times more FXa.[20] This catalytic effect of the procoagulant platelet on FVIII has also been confirmed in patients with severe HA. At the ISTH congress in 2022, Laha Roy et al. (2022) presented the results of their study, which included 12 patients with severe HA and an equivalent number of control subjects. Of the 12 patients with severe HA, 2 patients who received FVIII on demand had a mild bleeding phenotype with no muscle bleeds (and one had no joint bleeds).[21] The authors studied the activated platelets in the different patients, using flow cytometry to analyze monoclonal antibody for PAC-1 (anti-PAC-1) binding. This antibody recognizes the neoepitope of the active conformation of integrin GPIIb/IIIa on the surface of activated platelets. The analysis confirmed a higher anti-PAC-1 binding rate in the 2 severe HA patients with mild bleeding phenotype than in the control group (3.64% and 2.91% for the two severe HA patients with mild bleeding phenotype *versus* 0.95% in the control group).

Table 2. Observed parameters in the second 6-month study period with prophylactic rurioctocog alfa pegol in patients with hemophilia A

Parameters	Target FVIII trough level	
	1-3%	8-12%
Observed FVIII trough level, median	2.1-3%	10.7-11.7%
Total ABR, mean (SD)/median (Q1-Q3)	3.6 (7.5)/2.0 (0-4)	1.6 (3.4)/0 (0-2)
Spontaneous ABR, mean (SD)/median (Q1-Q3)	2.5 (6.6)/0 (0-4)	0.7 (1.7)/0 (0-0)
Joint ABR, mean (SD)/median (Q1-Q3)	2.6 (7.4)/0 (0-2)	1.1 (2.6)/0 (0-0)
Point estimates of the proportion of patients (%) with zero total bleeds, (95% CI)	42% (29-55%)*	62% (49-75%)*
Point estimates of the proportion of patients (%) with zero spontaneous bleeds, (95% CI)	60% (47-72%)†	76% (65-88%)†
Rurioctocog alfa pegol $T_{1/2}$ (hours), mean (SD)	15.3 (4.2)	14.7 (5.1)
Weekly infusions, median (Q1-Q3)	2 (2-2.3)	3.4 (3.1-3.6)
Weekly consumption (IU/kg), mean (SD)/median (Q1-Q3)	74.0 (31.8)/66.2 (51.3-96.3)	143.3 (56.2)/143.6 (91.4-189.8)

*p = 0.055.
†p = 0.055.
FVIII: factor VIII; ABR: annual bleeding rate; CI: confidence interval; IU: international units; Q1-Q3: interquartile ranges 1 and 3; SD: standard deviation; T½: plasma half-life.
Adapted from Klamroth et al[18].

Everything, therefore, seems to suggest that, in addition to plasma rFVIII levels, the increased or decreased affinity of rFVIII for the surface of activated platelets may play a key role in thrombin generation.

Simoctocog alfa is a fourth-generation rFVIII obtained from human cell line cultures without chemical modifications or protein fusion.[22] Vogel[23] analyzed the affinity of simoctocog alfa for the surface of activated platelets compared with other EHL-rFVIII (including efmoroctocog alfa, damoctocog alfa pegol, and rurioctocog alfa pegol). The various rFVIIIs were labeled with a fluorescent epitope and incubated at different equimolar concentrations with platelets extracted from healthy individuals, previously activated by thrombin. The latest results of the flow cytometry analysis presented by her group at the 16th Annual Congress of European Association for Hemophilia and Allied Disorders showed that simoctocog alfa had a significantly higher affinity than efmoroctocog alfa, damoctocog alfa pegol and rurioctocog alfa pegol for activated procoagulant platelets extracted from healthy individuals and incubated with equimolecular amounts of each of the tested rFVIII.[24]

Indirect comparisons may have their limitations, but in view of the lack of head-to-head studies in hemophilia, validated methods accepted by regulatory agencies, doctors, and payers have been developed to help balance the populations of the different studies in a comparable way.

Kessler et al.[25] used a matching-adjusted indirect comparison method to compare different personalized prophylaxis studies with PK-guided rFVIII. The results obtained with simoctocog alfa in the NuPreviq study that used a target rFVIII trough level of 1%[22] were compared with those of the A-LONG (efmoroctocog alfa with a target FVIII trough level of 1-3%),[26] Project VIII (damoctocog alfa pegol in randomized patients [30-40 IU/kg twice weekly, 45-60 IU/kg every 5 days, or 60 IU/kg every 7 days]),[27] and PROPEL studies (rurioctocog alfa pegol in patients randomized to two arms with target FVIII trough levels of 1-3% or 8-12%).[18] The percentage of patients with zero bleeds was found to be significantly higher with simoctocog alfa than with the other three rFVIII concentrates (Fig. 3A). Furthermore, the mean ABR with simoctocog alfa was significantly lower than with damoctocog alfa pegol (Fig. 3B). Finally, the mean weekly dose of simoctocog alfa was significantly higher than that of efmoroctocog alfa, damoctocog alfa pegol and rurioctocog alfa pegol (in the 1-3% target trough arm) and significantly lower than that of rurioctocog alfa pegol in 8-12% target trough arm (Fig. 3C).

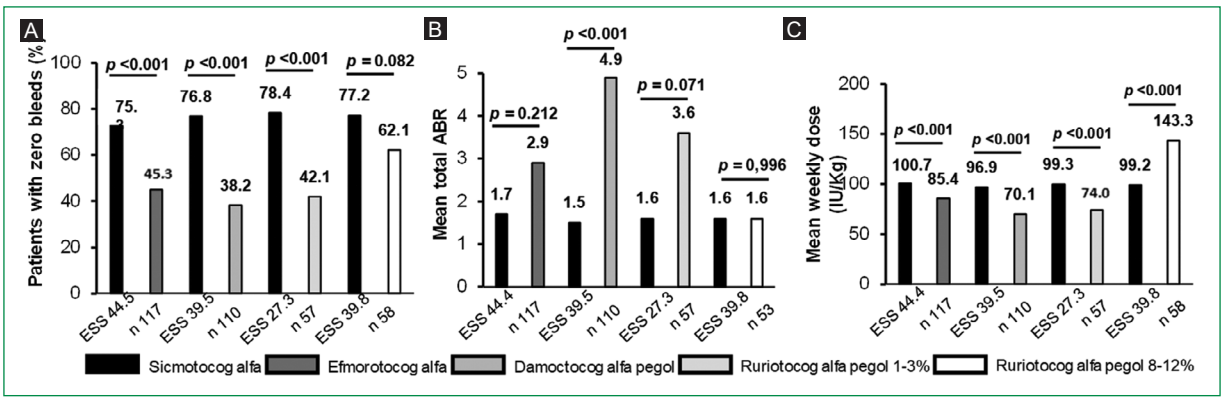

Figure 3. Matching-adjusted indirect comparison of simoctocog alfa *versus* efmoroctocog alfa, damoctocog alfa, and rurioctocog alfa *(adapted from Kessler et al.).*[25] The ESS for simoctocog alfa after matching the populations based on baseline characteristics were 44.4, 39.5, 27.3, and 39.8 for the matching-adjusted indirect comparison analyses with efmoroctocog alfa, damoctocog alfa pegol, and rurioctocog alfa pegol 1-3% and 8-12%, respectively. **A:** percentage of patients with zero bleeds. **B:** mean values for total ABR; **C:** mean weekly clotting factor dose. ABR: annual bleeding rate; ESS: effective sample size, IU: international units.

Conclusions

The primary objective in the management of hemophilia should be to prevent bleeding, which causes numerous comorbidities in patients in the mid to long term. Prophylaxis is currently the standard of care for patients with hemophilia, especially those with severe HA, and personalized treatment with FVIII concentrates is defined as the gold standard. However, the most recent evidence points toward the importance of extending the benefits of prophylaxis not only to patients with severe HA but also to patients with moderate and even mild HA, since it has been observed that lower disease severity is not a protective factor against hemophilic arthropathy. Consequently, there is still a population of patients whose needs are not met by the on-demand treatment that is still generally prescribed. It is vitally important to implement early prophylaxis in these patients and to continuously monitor joint status and evaluate treatment adjustments throughout their lifetime.

The definition of target trough levels can be somewhat complex since a standard trough objective of FVIII > 1% achieves a significant reduction in bleeding, but it is impossible to completely eliminate joint damage in all patients due to spontaneous bleeds. Therefore, prophylaxis must be tailored and adapted to the different stages in the patient's life, and doses and/or infusion frequency must be adjusted as appropriate to prevent bleeding.

In recent years, since the appearance of EHL concentrates, efforts have been primarily focused on reducing patient disease burden. While this is crucial in the treatment of hemophilia, it is also important to bear in mind patients' mid- to long-term QoL, a variable that is fundamentally affected by arthropathy and pain. The current objective of prophylaxis must therefore be more ambitious and move beyond converting severe disease to moderate or mild manifestations toward a goal of zero bleeds.

Plasma FVIII levels clearly play a key role in achieving this goal, but the way in which FVIII does its work is just as important as maintaining factor levels. Several studies suggest that FVIII-platelet binding may play a significant role in the procoagulant capacity of FVIII. Therefore, if we look beyond the PK parameters, the degree of FVIII adhesion to the surface of activated platelets could be a decisive factor in determining their functionality and selecting the most appropriate product. Thus, just as we target different trough levels depending on the type of patient (e.g., according to their age and procoagulant factor clearance), it would also be reasonable to select an rFVIII concentrate on the basis of its affinity for the procoagulant platelet and its ability to generate FXa. This question raises an interesting line of research.

In preliminary *in vitro* studies, simoctocog alfa has shown a statistically higher affinity for the surface of activated procoagulant platelets than other EHL products such as efmoroctocog alfa, damoctocog alfa pegol, and rurioctocog alfa pegol. This may explain the data from clinical trials that favor simoctocog in individualized prophylaxis compared to other EHL-rFVIII products. Simoctocog alfa is not an EHL product since it is produced without chemical modifications, although it has some interesting characteristics with respect to other EHL factors. Like these, it offers a reduced therapeutic burden in terms of the number of weekly infusions, although to reach similar target trough levels, a

somewhat higher weekly consumption is required. Even so, compared to other factor concentrates, simoctocog is currently the rFVIII that seems to offer greater protection against bleeding at similar target trough levels.

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None.

Conflicts of interests

M. Rodríguez-López received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or honoraria for consulting, and/or funds for research from Takeda, Octapharma, CSL-Behring, Novo Nordisk, Sobi, Roche and Pfizer. R.J. Núñez-Vázquez has received fees as a paid consultant from Novonordisk, Takeda, Grifols, Roche, Pfizer, Octapharma, CSL-Behring, and Sobi.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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SCIENTIFIC LETTER

Inhibitors in hemophilia B in the era of extended half-life FIX concentrates: a case report

Inhibidores en hemofilia B en la era de los concentrados de FIX de vida media extendida: a propósito de un caso

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Introduction

The development of inhibitors is currently recognized as the most important complication of replacement therapy in patients with hemophilia. In patients with hemophilia B (HB), the risk of developing an inhibitor is lower than in patients with hemophilia A (HA). The reported frequency of inhibitor development is less than 5% among all patients with HB and between 9% and 23% in cases with severe disease. Approximately 80% of the inhibitors that develop in HB are high-responding.[1]

Inhibitors develop as a consequence of a multifactorial process in which both genetic and non-genetic risk factors are involved; however, in HB – and probably due to the small number of patients who develop an inhibitor – there is limited information establishing a relationship between their occurrence and non-genetic risk factors.

Objective

To report the experience with the use of recombinant FIX concentrate fused to recombinant albumin in the management of a patient diagnosed with severe HB who, after developing an inhibitor and after three failed attempts at immune tolerance induction (ITI) therapy with standard half-life recombinant FIX concentrate (SHL-rFIX), including the use of immunosuppression, achieved complete success after switching to Idelvion® (albutrepenonacog alfa, an extended half-life FIX concentrate fused to recombinant albumin, rFIX-FP).

Case description

This is the case of a 17-year-old adolescent diagnosed with severe HB (FIX 0,6%) at 6 months of age in the context of a spontaneous cerebral hemorrhage. Intensive treatment with SHL-rFIX was initiated for 21 days, which required the placement of a first port-a-cath. After this period, the patient was discharged and recovered without sequelae. At that time, prophylaxis with SHL-rFIX was initiated at a dose of 40 IU/kg, 3 times per week. The result of the genetic study revealed a mutation (guanine deletion in exon 2 [nucleotide 6403] of the *F9* gene) resulting in a stop codon. During childhood, the patient exhibited a severe hemorrhagic phenotype with multiple bleeding episodes up to the age of 7 years, particularly in the left ankle, despite maintaining trough levels > 1-2%. Until that time, all inhibitor determinations had been persistently negative. At the age of 7 years, and after more than 500 exposure days (ED), a high-titer inhibitor was detected (32 Bethesda units [BU]) with type 2 kinetics. At that time, daily ITI therapy was initiated (dose of 100 IU/kg).

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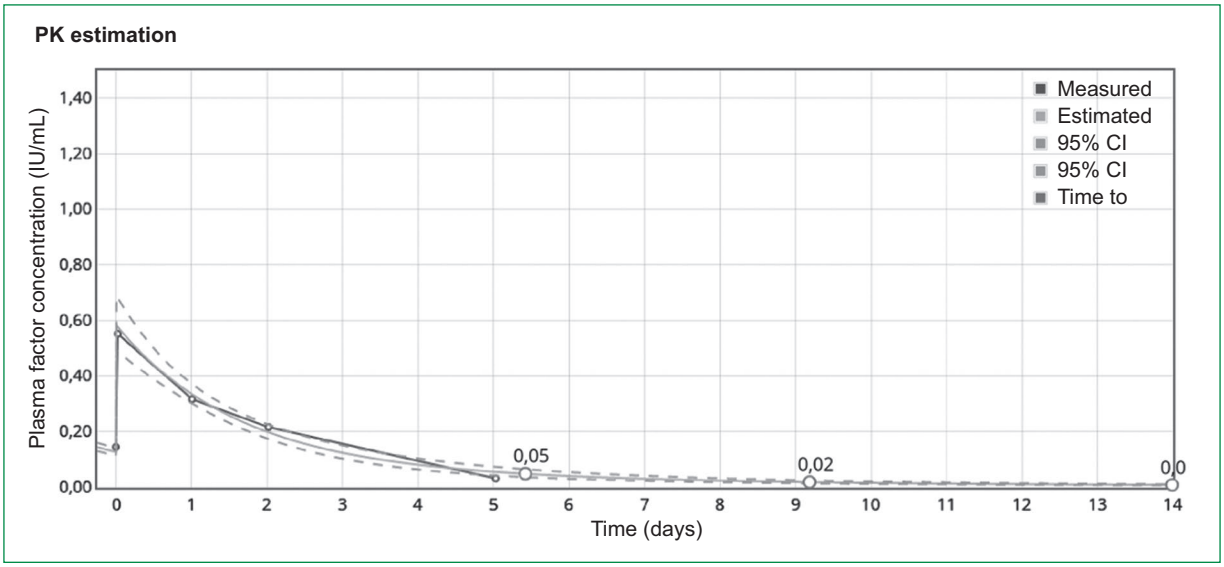


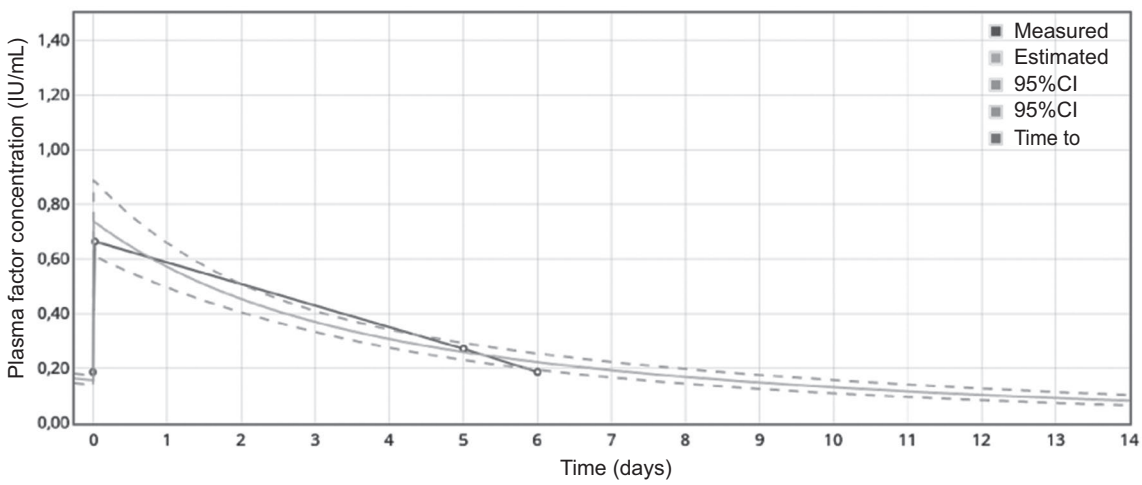
Figure 1. First pharmacokinetic evaluation with rFIX-FP (July 2023). Balanced estimation. CFIX: FIX concentrates; 95% CI: 95% confidence interval.

Analytical monitoring was scheduled every 4 weeks: 24-hour urine testing initially monthly and later quarterly, monthly biochemical analysis, urine dipstick testing after each administration (to monitor the appearance of proteinuria and signs of nephrotic syndrome), and monthly inhibitor determination. Approximately 6 months later, due to persistence of the inhibitor (8 BU), an anti-CD20 monoclonal antibody was added (4 doses; 375 mg/m^2/week), resulting in inhibitor negativization but without normalization of recovery or half-life (partial success). A gradual dose reduction was attempted until reaching 50 IU/kg every 48 h, at which point the inhibitor rebounded (4 BU). The SHL-rFIX dose was increased to 50 IU/kg/day and, 2 months later, the inhibitor was negative. Bleeding episodes were treated with recombinant activated FVII (when the inhibitor was positive) and with SHL-rFIX when it was negative. The year 2020 was particularly complicated. First, during removal of the port-a-cath due to infection, the patient developed an allergic reaction, although the causative agent could not be determined (antibiotic therapy used, SHL-rFIX, factitious urticaria). Therefore, a structured desensitization protocol was carried out by the Allergy Department. Second, the patient was proposed for participation in a clinical trial with a subcutaneously administered rebalancing agent, but was ultimately rejected because, according to the trial sponsor, the inclusion criteria were not met. After more than 4 years of daily administration of SHL-rFIX, in July 2023 mild proteinuria was detected in a 24-hour urine analysis (0,20 g/24 h; 0-0,15), confirmed 7 days later (0,30 g/24 h). After reviewing the literature,[2] we decided to switch to recombinant albumin-fused FIX (rFIX-FP) at a dose of 60 IU/kg (total, 3.000 IU), adjusted according to pharmacokinetics (WAPPS-Hemo®) every 5 days (plasma level at 120 h 3,3%, recovery at 30 minutes 66%) (Fig. 1). The patient presented accelerated clearance and a reduced half-life vs the estimates reported by Zhang et al.,[3] who suggested that with a dose of 50 IU/kg in a child older than 12 years, FIX levels > 5% should be maintained for 12,5 days, > 3% for 15,5 days, and > 1% for a total of 23 days.

After presenting two traumatic muscle hematomas within the first 2 months, in the context of sports practice (soccer), which responded well to the administration of two additional doses of 3.000 IU of rFIX-FP spaced 48 h apart, the infusion regimen was reduced to every 4 days for 2 months. Due to the patient's favorable clinical course and the progressively higher trough levels recorded, the infusion interval was gradually extended, remaining for 4 months on a regimen every 4 days and then for 6 months every 5 days. At 10 months, after documenting a trough level of 27%, weekly prophylaxis was initiated. At the 1-year follow-up, the patient can be considered to be "in remission"; with an infusion regimen of 55,5 IU/kg every 7 days, trough FIX levels of 18% were observed (recovery 88%) (Table 1 and Fig. 2) (for FT4, in children aged 12 to < 18 years, 88,8 h; 51,5-130,0). In addition, the patient has remained free of bleeding during the last

Table 1. Comparison between the balanced estimates of WAPPS-Hemo®

Parameter	Time to reach 0,05 IU/dL	Time to reach 0,02 IU/dL	Time to reach 0,01 IU/dL	Half-life
July 2023	130 h	220.5 h	335.75 h	78 h
September 2024	447.75 h	672.75 h	898 h	142.25 h



Infusion data used for this estimation

Identification	Drug	Total IU	IU/kg	End of infusion	CL	AUC (IU×h/L)
103761	Idelvion	3000	63,2	2024-07-10 09:00	0,042	71189

Elapsed time (hh:mm)	Before the dose	Plasma factor concentration (IU/mL)	Notes
-00:10	✔	0,188 UI/mL (18,8%)	
+00:30		0,665 UI/mL (66,5%)	
+120:00		0,273 UI/mL (27,3%)	
+144:00		0,188 UI/mL (18,8%)	

Figure 2. Pharmacokinetics with rFIX-FP (September 2024). Balanced estimation. AUC: area under the curve; CL: clearance; PK: pharmacokinetics; 95%CI: 95% confidence interval.

10 months, with a substantial improvement in quality of life and a degree of independence and autonomy that had not previously been achieved. The most recent joint evaluation performed using HEAD-US (October 2024) showed a score of 1, with synovial hypertrophy in the left ankle (the previous score in 2023 was 2). For the remaining joints, the score was 0.

Discussion

Risk factors for the development of inhibitors include the presence of large deletions (as in this patient) and null mutations in the *F9* gene, as well as early and intensive exposure to FIX concentrates, as occurred in our patient. Male et al.[5] described a cumulative incidence of inhibitors of 10,2% at 500 exposure days (ED) in a well-defined, unselected cohort of previously untreated patients with severe HB. Our patient developed the inhibitor after more than 500 ED despite having received intensive treatment at diagnosis.

ITI in patients with HB and high-titer inhibitors is performed less frequently than in patients with HA due to the lower success rate reported and the risk of severe complications such as anaphylactic reactions or the

Table 2. Pharmacokinetic comparison before and after 12 months following the initiation of prophylaxis with rFIX-FP

Date	Recovery	FIX levels	Predicted levels at 14-15 days (WAPPS, balanced)
July 2023	66%	At 120 h: 3,3%	1%
September 2024	88%	At 144 h: 18,8%	7.4%

rFIX-FP: recombinant FIX concentrate fused to recombinant albumin.

development of nephrotic syndrome. Therefore, the available evidence on inhibitor eradication in patients with HB is very limited, and management is generally carried out in a manner similar to that used for inhibitors against FVIII. At the same time, the criteria for defining immune tolerance success are not clearly established. On the other hand, new subcutaneously administered molecules such as Concizumab® or Mastarcimab®,[6,7] inhibitors of the tissue factor pathway, have demonstrated the safety and efficacy profile in preventing bleeding in patients with inhibitors in both HA and HB. In the field of HB, they could change the prognosis, even survival, of patients who develop inhibitors against FIX and are not candidates for ITI. They may even call into question the use of ITI in those few patients with HB who develop inhibitors against FIX.

Recently, Palomo Bravo et al.[8] reported their experience in the treatment of a pediatric patient who developed a high-titer inhibitor to SHL-rFIX associated with an anaphylactic reaction. In that case, successful immune tolerance induction without immunosuppression was achieved using very low doses of rFIX-FP that were gradually increased. In our case, this was the first report of such an experience, which encouraged us to proceed with the switch. Although several mechanisms involved in the development of inhibitors against FIX have been hypothesized, it has been suggested that mast cells present in the extravascular space, upon contact with extravasated FIX, could trigger an IgE-mediated hypersensitivity reaction.[9] The influence of the larger volume of distribution of SHL-FIX or complement activation due to the formation of transient IgG1 antibodies has also been proposed[10]. In the case of rFIX-FP, whose pharmacokinetics appear to follow a bicompartmental model,[4,11] the molecule shows a small volume of distribution and minimal extravascular distribution, which could reduce the risk of anaphylaxis. These allergic reactions have been associated with the development of nephrotic syndrome. Typically, this condition appears around 8 or 9 months after the start of ITI with high doses of FIX and presents with symptoms such as periorbital edema, proteinuria, hypoalbuminemia, and oliguria. Our patient had been receiving daily SHL-rFIX at doses of approximately 40-50 IU/kg/day for more than 4 years following desensitization, with regular 24-hour urine monitoring and urine dipstick testing after each infusion. Although it seemed unlikely, the mere "threat" (proteinuria confirmed by two determinations even in the absence of hypoalbuminemia or oliguria) was considered sufficient to propose a change of product. Although the etiology remains unknown, it appears to be related to immune complex deposition, although this has not yet been fully elucidated. In published cases, renal biopsy has described membranous glomerulonephritis without the presence of FIX immune complexes.[12] In some cases, the syndrome resolves after discontinuation of treatment with FIX concentrates (CFIX); in others, corticosteroid therapy has been required, and irreversible cases have also been reported.

The success of this individual case is evident: first, proteinuria disappeared and therefore the risk of developing nephrotic syndrome was reduced due to the lower dose received and the lower protein content of the new molecule. A progressive normalization of pharmacokinetic parameters was observed without inhibitor rebound. The first study, in July 2023, showed a recovery of 66%, FIX plasma levels of 3,3% at 120 h, and the balanced prediction in relation to FIX levels at 14 days was 1%. Pharmacokinetic evaluation one year later showed a recovery of 88,3%, FIX plasma levels of 18% at 144 h, and a predicted level at 15 days of 7,4%, values within the normal range for a patient of this age (Tables 1 and 2).

Furthermore, rFIX-FP achieved adequate clinical control and substantially reduced the treatment burden (approximately 80%). The economic cost decreased slightly, although the difference is expected to become more noticeable after one year of treatment. Nevertheless, this case is not generalizable; however, it is important to report experiences of this type to "open the door to new hypotheses regarding the doses required to achieve immune tolerance with other factor concentrates," as stated by Dr. Palomo Bravo.[8]

Conclusions

The management of patients with severe HB who develop inhibitors remains one of the major challenges

faced by healthcare professionals involved in their care. As with the publication by Palomo Bravo et al., this case reinforces the potential of rFIX-FP as a viable alternative for immune tolerance induction, highlighting the possibility of avoiding immunosuppression and the risk of its associated adverse effects in patients who develop complications such as anaphylactic reactions or a potential risk of nephrotoxicity. The experience obtained suggests that the use of extended half-life products could be key to improving clinical outcomes in difficult-to-treat patients through personalized therapies, reducing the need for frequent infusions and improving patients' quality of life. Further studies are needed to establish standardized protocols that include these extended half-life concentrates, similar to what has been done in HA with certain extended half-life FVIII concentrates, in the management of inhibitors in HB, especially in patients at high risk of immunological complications.

We believe that this case provides some evidence regarding its efficacy and safety, although we emphasize the need for future research and the development of treatment protocols.

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Conflicts of interest

None.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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