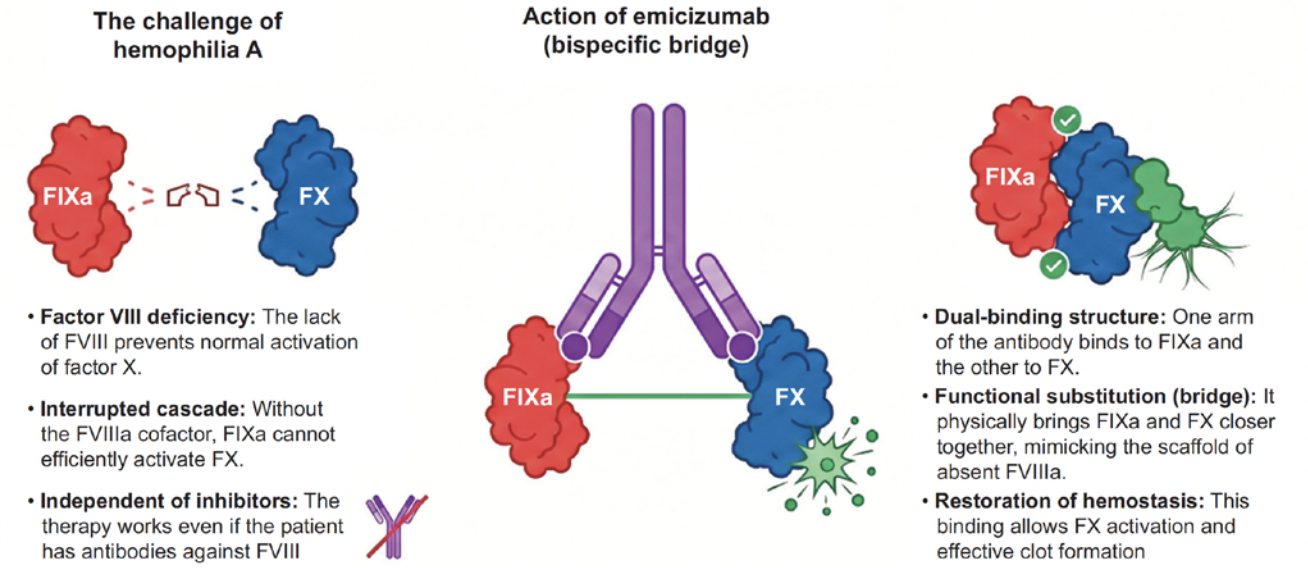
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Indexed en Bibliovigilance
ISSN: 2938-8740

Hemostasia y Trombosis

REVISTA IBEROAMERICANA DE TROMBOSIS Y HEMOSTASIA

Volume 3 • Number 2 • April-June 2026



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EDITORIAL

Clinical decision-making beyond the threshold of classification in bleeding coagulation disorders

La decisión clínica más allá del umbral de la clasificación en las coagulopatías hemorrágicas

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In the classical view, medicine requires classification to understand and make decisions. Thus, we speak of severe, moderate, or mild hemophilia; congenital or acquired diseases; plasma-derived or recombinant products; and response, failure, or remission. This nomenclature enables us to organize knowledge, compare outcomes, and develop recommendations. However, no classification fully encompasses reality or anticipates the scenarios that may arise during the course of a disease. A classification is only a starting point: 2 patients assigned the same label may follow profoundly different clinical trajectories and have markedly different needs and risks.

This issue of *Hemostasia y Trombosis: Revista Latinoamericana de Trombosis y Hemostasia* focuses on bleeding disorders, particularly hemophilia, at a time when the emergence of promising therapeutic alternatives has clearly broadened the options available for clinical decision-making. When few options existed, the diagnostic category led almost directly to the treatment that should be prescribed. Currently, with concentrates possessing different properties, and rebalancing therapies, new indications for prophylaxis, and the introduction of gene therapy, disease classification continues to guide us, but it is no longer sufficient. Beyond this threshold, other variables become increasingly important, including bleeding phenotype, disease trajectory, comorbidities, pharmacokinetics, age and general health status, immunologic risk, and patient preferences.

The experience of the first patient treated in Spain with etranacogene dezaparvovec exemplifies this change. A diagnosis of severe hemophilia B makes it possible to identify potential candidates, but it does not determine, *per se*, who should receive gene therapy. In the case presented in this issue,[1] the therapy made it possible to discontinue prophylaxis and achieve factor IX activity close to 50% at 3 months, with no further bleeding episodes. Nevertheless, the elevation in transaminase levels and the need for corticosteroid therapy demonstrate that the outcome cannot be summarized solely by a factor level. Experience with gene therapy in hemophilia B shows that meeting regulatory criteria is not enough. Candidate selection must take into consideration the patient's liver status, ability to adhere to demanding follow-up, and expectations. Patient motivation, hepatic and psychological assessment, and the center's capacity to provide close

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Date of reception: 01-07-2026
Date of acceptance: 14-07-2026
DOI: 10.24875/RHT.M26000096

Available online: 03-09-2026
Hemost Trombos (Eng). 2026;3(2):35-37
www.revistahemostasiaytrombosis.com

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follow-up are fundamental components of treatment understood as comprehensive medical care.

This issue of the journal also leads us to a more traditional question: who needs prophylaxis? The study by Rodríguez-Esteban et al.[2] shows that the distinction between severe, moderate, and mild hemophilia based solely on baseline factor activity does not always reflect the severity of the clinical condition and, consequently, the need for prophylaxis. Severity defined according to baseline factor level may underestimate the true burden of disease, and additional assessment of bleeding history, joint damage, physical activity, and quality of life may justify a more intensive preventive strategy. A patient may be classified as "moderate" on the basis of laboratory findings yet experience a clinical burden that warrants a preventive strategy characteristic of "severe" disease. In a series of patients with nonsevere forms of hemophilia, prophylaxis reduced the annualized bleeding rate by more than 90% and virtually eliminated emergency visits for bleeding. In this setting, the factor level did not change, but the interpretation of its significance did. Hemarthroses, pain, joint damage, physical activity, and dependence on hospital care place some patients beyond what may be indicated by a classification based solely on laboratory data.

Classification processes may inadequately describe changes and intercurrent events arising in clinical practice. This is illustrated by the case reported in this issue of a young patient with mild hemophilia A who developed a high-titer inhibitor after intensive exposure to factor VIII.[3] A disease managed for years as mild therefore abruptly acquired a much more complex bleeding phenotype, demonstrating that an initially favorable category is not immutable. The case reminds us that "mild" describes a level of factor activity but does not eliminate risks, such as immunologic risk, which may persist throughout life. In these cases, therapeutic decisions must also integrate bleeding severity, the risk of recurrence, and treatment toxicity.

Moreover, the increasing life expectancy of people with hemophilia requires decisions in areas for which traditional classifications provide few answers. Prasca et al.[4] describe the endovascular treatment of an intracranial aneurysm in a patient with severe hemophilia A who required dual antiplatelet therapy. The difficulty lay not in identifying or classifying the 2 diseases, but in making their treatments compatible. In the absence of specific recommendations, individual pharmacokinetic data were used to maintain adequate factor VIII trough levels during the period of greatest risk. This case demonstrates that the hemostatic target must be adjusted to the concomitant risk and modified whenever that risk changes.

Another example of a delicate balance is found in the patient described with acquired hemophilia A.[5] The 90-year-old patient had colorectal cancer, postoperative bleeding, and a high-titer inhibitor, simultaneously combining frailty, bleeding risk, and thrombotic risk. The decision did not involve choosing between hemostasis and inhibitor eradication, but rather separating the 2 objectives over time. Emicizumab created a window of protection, although this advantage must be balanced against thrombotic risk, cost, and the absence of an approved indication in most countries.

Furthermore, classification affects therapeutic products. The term von Willebrand factor concentrates encompasses preparations with different compositions, different ratios of von Willebrand factor to factor VIII, and different pharmacokinetic profiles. The article by Salvado et al.[6] analyzes how these differences may influence thrombin generation, factor VIII accumulation, and thrombotic risk. Although indirect comparisons require caution, the study shows that selecting a concentrate does not simply involve replacing a given amount of protein. It is also important to assess how its components interact, when they reach peak levels, and how they behave after repeated exposure. The name identifies the product, but its pharmacology helps determine how it should be used.

A similar consideration applies to viral safety. The term "plasma-derived" inevitably retains the memory of infections transmitted during the last century. However, the review published in this issue[7] shows that the origin of a product cannot be used as a substitute for a genuine risk assessment. Donor selection, molecular screening, purification, and successive viral inactivation or removal steps have made it possible to achieve unprecedented levels of safety. The importance of sustained pharmacovigilance must be emphasized. The absence of confirmed transmissions in modern series does not mean that surveillance is unnecessary; rather, it is precisely the result of maintaining such surveillance. Safety does not reside in a label, but in the robustness of the process underlying it.

Finally, the study of avatrombopag in immune thrombocytopenia extends this same reflection.[8] The efficacy of a thrombopoietin receptor agonist could be classified according to the platelet count response, but this measure does not fully reflect its clinical value. In the 22 patients analyzed, avatrombopag produced a sustained increase in platelet count, enabled a reduction in concomitant treatments, and decreased the mean

weekly cost per patient by approximately 62%. Although the limitations of a single-center series require the magnitude of the economic effect to be interpreted cautiously, resource use is also part of clinical decision-making. A treatment does not fully achieve its objective when its benefit is difficult to sustain for either the patient or the healthcare system.

The studies gathered in this issue do not question the need for or usefulness of classification. Classification remains the language through which we recognize disease, conduct research, and build shared knowledge. What these studies demonstrate is that clinical medicine must adapt when reality extends beyond that initial description. The threshold is therefore not the point at which classification loses its value, but the point at which it ceases to be sufficient. Before that threshold is crossed, the category provides guidance and indicates the path forward; beyond it, biology, disease course, and context must guide the decision.

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ORIGINAL RESEARCH ARTICLE

Gene therapy with etranacogene dezaparvovec in haemophilia B: about the 1st patient infused in Spain

Terapia génica con etranacogene dezaparvovec en hemofilia B: a propósito del primer paciente infundido en España

Manuel Rodríguez-López[1], Elena Y. Romero-Ventosa[2], Antia Amoedo-Bastos[1], Raquel Iglesias-Varela[1], María E. López-Ansoar[1], Paula Sar-Fuentes[1], Raquel Ocampo-Martínez[1], and Carmen Albo-López[1]*

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Abstract

Introduction: *Etranacogene dezaparvovec (ED) is the first gene therapy approved in Europe for severe or moderately severe haemophilia B without inhibitors. Its implementation in Spain began in 2024 as an alternative to conventional FIX prophylaxis.* **Objective:** *To describe the initial clinical experience and 3-month outcomes of the first patient treated with ED in Spain, in the context of the 5-year HOPE-B data.* **Materials and methods:** *Data collection from the patient's electronic medical record.* **Results:** *A 41-year-old male with baseline FIX 1.6% and advanced arthropathy received a single intravenous dose of ED. Infusion was well tolerated, with immediate discontinuation of prophylaxis. FIX activity increased progressively to 49.9% at 3 months, placing the patient at the 67th percentile of the HOPE-B trial (mean 39.0 IU/dl at month 6; 36.1 ± 15.7 IU/dl at 5 years). Mild and transient transaminitis was managed with prednisone without additional complications.* **Conclusions:** *Initial results confirm the expected safety and efficacy of ED in real clinical practice, consistent with the long-term HOPE-B profile, and highlight the importance of careful patient selection and motivation.*

Keywords: *Haemophilia B. Gene therapy. Etranacogene dezaparvovec. Factor IX coagulative activity.*

Resumen

Introducción: *Etranacogene dezaparvovec (ED) es la primera terapia génica aprobada en Europa para hemofilia B grave o moderadamente grave sin inhibidores. Su implementación en España comenzó en 2024 como alternativa a la profilaxis convencional con factor IX (FIX).* **Objetivo:** *Describir la experiencia clínica inicial y los resultados a tres meses del primer paciente tratado con ED en España, en el contexto de los datos de 5 años del ensayo HOPE-B.* **Material y métodos:** *Recogida de datos de la historia clinica electronica del paciente.* **Resultados:** *Varón de 41 años, FIX basal 1,6% y artropatía avanzada, recibió una dosis única intravenosa de ED. La infusión fue bien tolerada con suspensión inmediata de la profilaxis. La actividad de FIX aumentó progresivamente hasta el 49,9% a los tres meses, situando al paciente en el percentil 67 del ensayo HOPE-B (media 39,0 UI/dl al mes 6; 36,1 ± 15,7 UI/dl a los 5 años). Se observó transaminitis leve y transitoria, controlada con prednisona, sin complicaciones adicionales.* **Conclusiones:** *Los resultados initialers confirman la seguridad y eficacia esperadas de ED en práctica clínica real, consistentes con el perfil a largo plazo del HOPE-B, y subrayan la importancia de una selección cuidadosa y la motivación del paciente.*

Palabras clave: *Hemofilia B. Terapia génica. Etranacogene dezaparvovec. Factor IX coagulativo.*

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Date of reception: 28-09-2025
Date of reception: 03-06-2026
DOI: 10.24875/RHT.M26000094

Disponible en línea: 03-09-2026
Hemost Trombos (Eng). 2026;3(2):38-43
www.revistahemostasiaytrombosis.com

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Introduction

Etranacogene dezaparvovec (ED) is the first gene therapy approved by the European Medicines Agency (EMA) in 2023 for adult patients with severe or moderately severe haemophilia B (HB) (factor IX [FIX] ≤ 2%) without inhibitors, based on the results of the HOPE-B clinical trial.[1] In Spain, it has been available since September 2024 following approval by the Interministerial Commission on Medicine Prices.[2] At present, there is no national reference network for infusion centres, as proposed by the EAHAD (European Association of Haemophilia and Allied Disorders) and the UKCHDO (United Kingdom Haemophilia Centre Doctors' Organisation),[3,4] which advocate the implementation of a hub-and-spoke model with clearly defined functions.

ED is expected to provide long-term functional correction of HB by enabling endogenous FIX production after a single intravenous administration. Data from the final 5-year HOPE-B analysis.[5] (published in December 2025 in the *New England Journal of Medicine*) confirm that a single dose of ED induced durable and effective FIX Padua expression for 5 years in patients with severe or moderately severe HB. In the full analysis population (n = 54), the overall annualised bleeding rate (ABR) was 4.16 during the lead-in period and 1.52 during months 7–60 after gene therapy, representing a 63% reduction (95%CI, 24–82). Mean endogenous FIX activity remained stable throughout the 5-year follow-up, with a value of 36.1 ± 15.7 IU/dl at year 5; 80% of participants had FIX activity ≥ 12 IU/dl at that time (Fig. 1). Exogenous FIX consumption was reduced by 96%, from 257,339 IU/year during the lead-in period to 10,924 IU/year during months 7–60. A total of 94% of participants (51/54) discontinued continuous FIX prophylaxis without restarting it during the 5-year follow-up. No FIX inhibitors or thrombotic events were detected during the analysis period.

Despite the high cost of treatment, the adoption of outcome-based payment models appears to be a reasonable strategy, as it makes the initial economic impact on public health systems more flexible. Durability of FIX expression for up to 20–25 years has been estimated for > 80% of recipients, according to Bayesian models,[6] which require confirmation with prospective longitudinal data. This estimate is consistent with the results of the AMT-060 study,[7] the precursor platform of ED, which uses the wild-type FIX transgene instead of the Padua variant, with stable FIX levels at 8 years – although around 5%, lower than those achieved with ED – confirming the long-term feasibility and safety of the AAV5 platform.

Method

We describe the initial clinical experience and 3-month outcomes of the first patient treated with ED in Spain. Clinical data were obtained from the electronic medical record and laboratory reports. The study was approved by the centre's Research Ethics Committee, and written informed consent was obtained.

Results

The patient was a 41-year-old man with moderately severe HB (baseline FIX 1.6%; genotype c.892C>T, exon 8, F9 gene, pathogenic variant generating a stop codon) receiving secondary prophylaxis with eftrenonacog alfa (50 IU/kg weekly) since 2018, with no current or previous history of FIX inhibitors. The patient had advanced haemophilic arthropathy (HEAD-US score: 7), predominantly affecting the ankles and left elbow. Baseline characteristics are shown in table 1.

Before requesting authorisation for infusion, compliance with all inclusion criteria and none of the exclusion criteria was certified, in accordance with the Therapeutic Positioning Report of the *Agencia Española de Medicamentos y Productos Sanitarios* (AEMPS).[8] The patient had a past medical history of resolved hepatitis C virus (HCV) infection, with liver stiffness by FibroScan of 3.1 kPa and normal abdominal ultrasound. Anti-AAV5 antibody titres were < 18.5 (lower limit of detection, AAV5 NAb Test Precision for Medicine®) in 2 determinations performed 2 months apart. Serology for the remaining hepatotropic viruses and HIV tested negative. Baseline liver biochemistry parameters and creatine phosphokinase (CPK) were normal.

Before signing the informed consent form, after delivery of the Gene Therapy Questions and Answers Guide for patients[9] and following the roadmap described by Álvarez-Román et al.,[10] the patient was evaluated by the clinical psychologist, who certified that he understood the process and his obligations. The informed consent form was prepared jointly by the Departments of Haematology and Pharmacy, with special emphasis on postinfusion obligations, including prohibition of alcohol consumption and use of barrier methods within the first year.

On 18 June 2025, the patient was admitted to the haematology unit. After confirming the absence of contraindications, ED was administered at a dose of

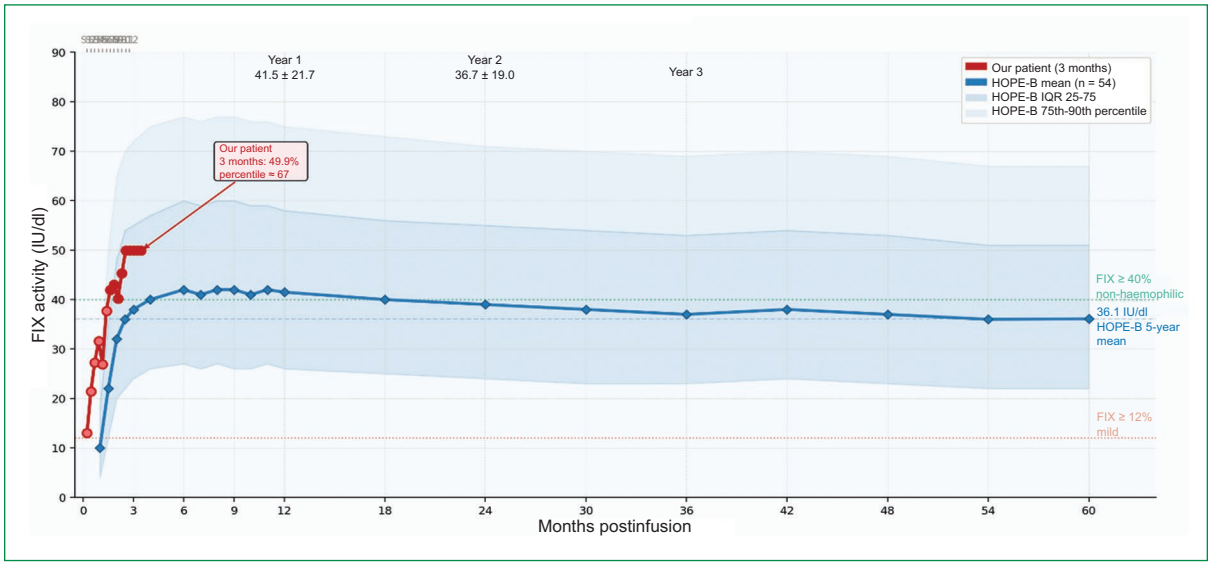


Figure 1. Endogenous FIX levels: our patient vs the HOPE-B trial (5-year follow-up) (*adapted from Pipe et al.*[5]). Comparison of endogenous FIX activity (IU/dL) between our patient (red line, circles) and participants in the HOPE-B trial (n = 54) within the 5-year follow-up. Blue line: HOPE-B arithmetic mean. Dark blue band: IQR (P25-P75). Light blue band: 75th–90th percentile. Reference lines: FIX ≥ 40 IU/dL (green dotted line, non-haemophilic threshold), FIX ≥ 12 IU/dL (orange dotted line, mild haemophilia threshold), HOPE-B mean at year 5: 36.1 IU/dl (blue dashed line). The upper axis shows the correspondence in weeks within the first 3 months. The annotation indicates the position of our patient at week 15 (FIX 49.9%, percentile ≈ 67). FIX: factor IX.

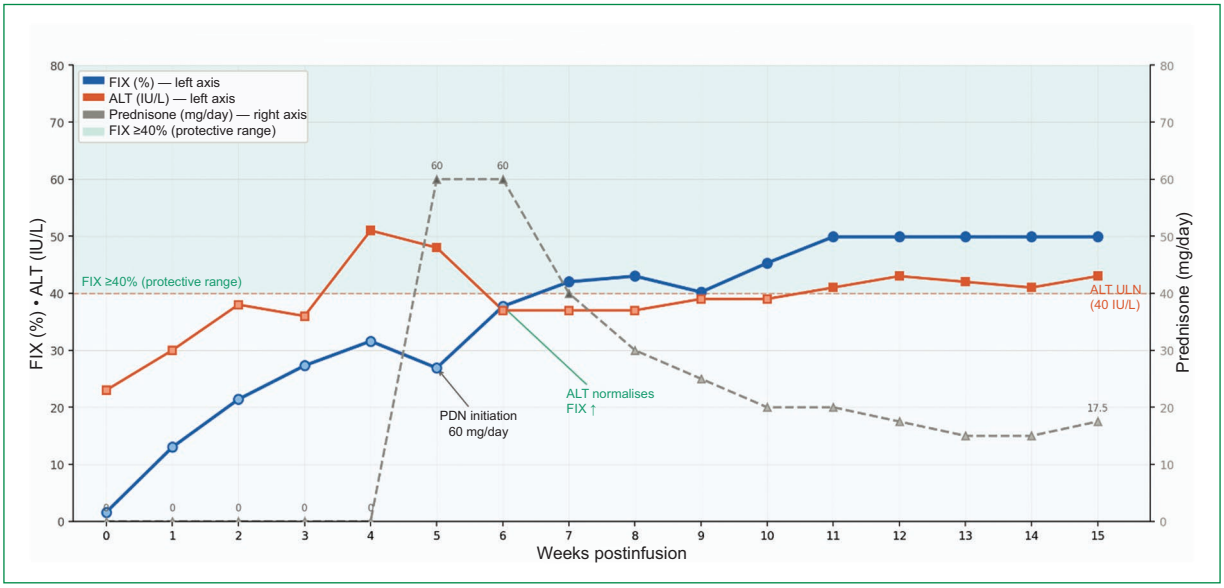


Figure 2. Evolution of FIX activity, ALT, and PDN dose (weeks 0-15 postinfusion). Weekly evolution of FIX activity (%) (blue line, circles; left axis), ALT (IU/l) (orange line, squares; left axis), and PDN dose (mg/day) (grey dashed line, triangles; right axis) during the first 15 weeks postinfusion of etranacogene dezaparvovec. The shaded green area indicates the FIX ≥ 40% range (protective range). The orange dashed line indicates the ALT ULN (40 IU/l). Dark blue FIX points: ≥ 40%. Light blue FIX points: < 40%. ALT: alanine transaminase; FIX: factor IX; PDN: prednisone; ULN: upper limit of normal.

Table 1. Patient baseline characteristics

Parameter	Value
Age	41 years
Sex	Male
Diagnosis	Moderately severe haemophilia B
Baseline FIX activity	1.6% (one-stage clotting assay)
F9 genotype	c. 892C > T, exon 8 – stop codon (moderately severe/severe phenotype)
Previous prophylaxis	Eftrenonacog alfa 50 IU/kg/week since 2018
Anti-FIX inhibitors	Negative (no history)
Haemophilic arthropathy	Advanced (HEAD-US: 7); ankles and left elbow
Previous HCV infection	Resolved. FibroScan: 3.1 kPa. Normal abdominal ultrasound
Hepatotropic virus and HIV serology	Negative
Anti-AAV5 antibodies	< 18.5 (negative; AAV5 NAb Test Precision for Medicine®; 2 determinations)
Baseline liver function	Normal ALT, AST, GGT, and bilirubin levels
Baseline CPK	Normal
Psychological evaluation	Suitable; understands postinfusion risks and obligations
Informed consent	Signed after multidisciplinary evaluation
Infusion date	18 June 2025
Dose administered	2×10^{13} gc/kg intravenously

AAV5: adeno-associated virus type 5; ALT: alanine transaminase; AST: aspartate transaminase; CPK: creatine phosphokinase; FIX: factor IX; gc: genome copies; GGT: gamma-glutamyl transferase; HCV: hepatitis C virus; HIV: human immunodeficiency virus.

2×10^{13} gc/kg intravenously over 1 h. The infusion was well tolerated, with no adverse events. EHL-FIX prophylaxis was discontinued on the same day. The patient remained under observation and was discharged 4 h later, with weekly follow-up visits initiated according to the centre's protocol, based on international recommendations and the product's summary of product characteristics.

Within the first days after administration, the patient reported greater tiredness than usual, remained afebrile, and experienced transient headache and myalgia within the first 24 h. These symptoms did not prevent him from carrying out his work activity and did not require specific management. From week 1 to week 4, FIX activity progressively increased from 13 to 31.6% (one-stage clotting assay, HemosIL SynthASil®, ACLTop®), while alanine transaminase (ALT) levels remained within the normal range.

At week 4, ALT increased to 51 IU/L (upper limit of normal [ULN]: 40 IU/L; last baseline value: 30 IU/l on 6 June 2025), with normal aspartate aminotransferase (AST), total bilirubin, and CPK. Forty-eight hours later, ALT spontaneously decreased to 41 IU/L, with a slight decrease in FIX to 28.3% – below the critical threshold of 20–30%. Four days later, ALT increased again to 48 IU/L and FIX decreased to 26.9%, a 15% decrease from peak, with all other parameters remaining normal. In accordance with our protocol and the HOPE-B data, interpreting the sustained increase in ALT as an immune response against the gene vector, prednisone 60 mg/day was started. After 7 days (week 6 postinfusion), ALT normalised and FIX increased to 37.7%.

Thereafter, prednisone was progressively reduced to 40 mg/day, with weekly clinical and laboratory follow-up. At week 15, FIX was 49.9%, ALT was 43 IU/L, and the prednisone regimen was 20–15 mg on alternate days. No bleeding episodes have occurred and no FIX concentrate administration has been required up to the closing date of this report (Fig. 2). Laboratory determinations are always performed using the same equipment to minimise variability in longitudinal follow-up.

Conclusions

We report the first 3 months of follow-up after the first ED infusion performed in Spain. Although the follow-up period is still short, treatment evolution has been successful to date. The patient reports a high degree of satisfaction, despite the demanding follow-up programme with weekly visits during the first months, which will continue until corticosteroid therapy is discontinued. The patient's strong motivation for gene therapy is a factor that we consider essential in candidate selection. Unlike the roadmap described by Álvarez-Román et al.,[10] in our case, a hepatologist was not included in the multidisciplinary team because the previous liver assessment was normal.

Infusion tolerance was excellent, in line with the HOPE-B safety profile, in which only 1 patient (1.9%) discontinued the infusion because of an infusion reaction, receiving only 10% of the planned dose.[5] Postinfusion symptoms – fatigue, headache, and myalgia during the first 24 h – correspond to those listed as very common (≥ 10%) in the summary of product

characteristics, are self-limiting, and do not require additional measures. The 3-month course follows the expected pattern: good infusion tolerance, mild and reversible elevation of liver enzymes, and satisfactory FIX levels. In HOPE-B, detectable FIX activity appears during the first week postinfusion, with a progressive increase and a stable plateau around weeks 6–8. Mean endogenous FIX was 41.5 ± 21.7 IU/dL (median: 39.9; range: 5.9–113) at year 1, 36.7 ± 19.0 IU/dL at 2 years,[11] and 36.1 ± 15.7 IU/dL at year 5,[5] showing remarkable stability over time (Fig. 1). Our patient's levels (49.9% at week 15) are consistent both in the dynamics of increase and in magnitude, placing him at approximately the 67th percentile of the pivotal trial. The final 5-year HOPE-B analysis further confirms that 96% of responding participants (51/52) maintained durable protection against bleeding during months 7–60 without restarting prophylaxis.

Regarding laboratory monitoring, the one-stage clotting assay is the recommended method in clinical practice for follow-up of patients with HB after gene therapy with FIX Padua.[12] Astermark et al.[12] emphasise that this method is appropriate and reliable – unlike the chromogenic assay, which tends to underestimate FIX activity – and that the same reagent should always be maintained to reduce longitudinal variability. At our centre, we use HemosIL SynthASil®, for which the authors report better agreement between central and local laboratories.

The observed transaminitis is consistent with a specific hepatocyte-mediated immune response against the AAV5 vector or the expressed transgene, without multiorgan or muscular damage, as reflected by normal AST, CPK, and bilirubin levels. In the 5-year HOPE-B analysis,[5] early ALT elevations – defined as an increase ≥ 2 × baseline level or > ULN within the first 4 months – were observed in 11 participants (20.4%), of whom 9 (16.7%) received systemic glucocorticoids for a mean of 81.4 ± 28.6 days (range 51–130). The incidence of these elevations was lower than that observed in previous trials of liver-directed gene therapy with AAV vectors. Importantly, participants with early ALT elevation had slightly lower mean FIX levels in the long term – although still within the therapeutic range – than those who did not develop it. Corticosteroid management in our patient is within the expected range and was not associated with worse prognosis in the pivotal trial. The French series[13] reported transient ALT elevations in 2 of 3 infused patients, without the need for corticosteroids. Immunosuppression in our patient is being adapted according to clinical and laboratory evolution.

From the standpoint of long-term safety, the final 5-year HOPE-B analysis[5] detected no evidence of treatment-related oncogenicity, late liver dysfunction, or thromboembolic events. The hepatocellular carcinoma diagnosed in 1 participant was determined not to be related to ED after independent molecular analysis of vector integration. This safety profile is particularly relevant given that more than half of HOPE-B participants had positive serology for HCV or hepatitis B virus (HBV) at screening, a situation also present in our patient, who had resolved HCV infection.

In parallel, a group of Spanish haematologists has begun developing an artificial intelligence platform aimed at selecting and monitoring patients who are candidates for gene therapy for HB (https://codigorojo.tech/home/), in line with the findings reported by Succi et al.[14] on the potential of AI for clinical training in rare diseases. To date, the system's recommendations are concordant with those of the clinicians involved.

In conclusion, ED administration in the first Spanish patient has proven safe and effective at 3 months of follow-up, with FIX expression in the therapeutic range, absence of bleeding, and successful management of transaminitis with corticosteroids. These results are fully consistent with the pattern of efficacy and safety confirmed by the final 5-year HOPE-B analysis. Selection of motivated and well-informed patients may be a determining factor for the success of this treatment. Long-term follow-up will make it possible to confirm the durability of response.

Funding

None declared.

Conflicts of interest

None declared.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The authors obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymised clinical data. Following to the nature of the study, individual informed consent was not

required. The relevant ethical recommendations were followed.

Declaration on the use of artificial intelligence. The authors declare that OpenAI was used for figure 1.

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ORIGINAL RESEARCH ARTICLE

Avatrombopag: beyond efficacy: experience of a center

Avatrombopag: más allá de la eficacia: experiencia de un centro

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Abstract

Introduction: *Thrompopoietin receptor agonists (TPO-RAs) have transformed the treatment of ITP. Avatrombopag, a second-generation oral TPO-RA, demonstrated superiority over placebo in clinical trials.* **Objective:** *To evaluate the efficiency of the use of avatrombopag in a tertiary care hospital.* **Material and methods:** *Retrospective analysis of 22 patients with ITP treated with avatrombopag.* **Results:** *Sixty-eight-point two percent had primary ITP; 81.8% had received other TPO-RA. Significant improvement in platelet count was observed (from 51,000/µl to > 140,000/µl; p = 0.0018). The final mean dose was 143.97 mg/week, reduced in specific subgroups. Average weekly cost per patient decreased by 62.45% (from € 703 to € 264).* **Conclusions:** *The study reveals a favorable clinical and economic impact. Reduction of doses and concomitant treatment suggests greater therapeutic efficiency in early stages. Avatrombopag shows high clinical efficacy and a notable cost reduction in ITP.*

Keywords: *Avatrombopag. Idiopathic thrombocytopenic purpura (ITP). Efficacy. Cost-effectiveness. Thrombopoietin agonists (TPO-RA).*

Resumen

Introducción: *Los agonistas del receptor de trombopoyetina (TPO-RA) han transformado el tratamiento de la púrpura trombocitopénica idiopática (PTI). El avatrombopag, un TPO-RA oral de segunda generación, demostró superioridad frente al placebo en ensayos clínicos.* **Objetivo:** *Evaluar la eficiencia del uso de avatrombopag en un hospital de tercer nivel.* **Material y métodos:** *Análisis retrospectivo de 22 pacientes con PTI tratados con avatrombopag.* **Resultados:** *El 68,2% tenía PTI primaria, el 81,8% habían recibido otros TPO-RA. Se observó mejora significativa del recuento plaquetario (de 51.000/µl a > 140.000/µl; p = 0,0018). La dosis media final fue de 143,97 mg/semana, reducida en subgrupos específicos. El coste semanal medio por paciente disminuyó un 62,45% (de 703 a 264 €).* **Conclusiones:** *El estudio revela un impacto clínico y económico favorable. La reducción de dosis y del tratamiento concomitante sugiere mayor eficiencia terapéutica en etapas tempranas. El avatrombopag muestra una alta eficacia clínica y una notable reducción de costes en la PTI.*

Palabras clave: *Avatrombopag. Púrpura trombocitopénica idiopática (PTI). Eficacia. Coste-efectividad. Agonistas de trom-bopoyetina (TPO-RA).*

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Date of reception: 09-06-2025
Date of accpetance: 16-07-2025
DOI: 10.24875/RHT.M25000076

Available online: 03-09-2026
Hemost Trombos (Eng). 2026;3(2):44-50
www.revistahemostasiaytrombosis.com

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Introduction

Thrombopoietin receptor agonists (TPO-RAs), currently considered first-choice second-line drugs for the treatment of this condition.[1] have radically changed the therapeutic management of idiopathic thrombocytopenic purpura (ITP) and have provided an effective and safe therapeutic alternative for a large number of patients. Among these agents, the most recently introduced, avatrombopag (*Laboratorios Sobi*), a second-generation oral TPO-RA, was approved by the European Medicines Agency (EMA) in 2021 for use in the treatment of chronic ITP in adults, pending completion of studies in pediatric patients. In the multicenter, randomized, double-blind study by Jurczak et al.,[2] which included an open-label extension phase, the safety and efficacy of avatrombopag were evaluated in adults with chronic ITP and low platelet counts ($< 30 \times 10^9$/L). When avatrombopag (20 mg/day) was compared with placebo over 6 months, with the possibility of entering an open-label extension phase, avatrombopag showed significant superiority in weeks with platelet response: median 12.4 weeks vs. 0 in the placebo group ($p < 0.0001$). A total of 65.6% of patients achieved a response by day 8 vs. 0% with placebo ($p < 0.0001$), and a reduction in concomitant medication was observed in 33.3% of the avatrombopag group vs. 0% in the placebo group. In addition, durable response was greater in the avatrombopag group (34.4 vs. 0% in the placebo group; $p = 0.009$). Overall, avatrombopag demonstrated efficacy and good tolerability for the treatment of chronic ITP. The safety and efficacy shown during clinical development have been corroborated by real-world studies published to date, such as the Spanish AVESPA experience.[3] We conducted a retrospective, multicenter study based on data from 28 Spanish hospitals from the *Grupo GEPTI (Grupo Español de Púrpura Trombocitopénica Idiopática)*, which included 268 patients with primary or secondary ITP, with varying degrees of severity and disease duration, followed until April 2024. The efficacy of avatrombopag was high: 92.2% achieved response ($\geq 50 \times 10^9$/L), regardless of treatment line, with a 79% response rate in patients in the 4th line or later, and a median time to response of 13 days (IQR, 7-21), which is consistent with that reported in the clinical trial. Response was not significantly influenced by age, sex, ITP duration, or prior exposure to eltrombopag/romiplostim. The drug proved highly safe; only 4.5% of patients discontinued treatment due to adverse events, which were not reported in up to 64.2% of participants. Furthermore, regarding the frequently mentioned thrombotic risk, the incidence rate of thromboembolic events was only 4%, which is lower than the 7% reported in the product's summary of product characteristics.[4] This is undoubtedly a study with substantial strength derived from its sample size, long follow-up period, and inclusion of patients who had previously failed several lines of therapy. An indirect comparison performed using generative artificial intelligence between avatrombopag and fostamatinib showed that the choice of one drug or the other may depend not only on clinical factors but also on patient preferences and economic considerations. In this regard, ChatGPT-4o would identify an initial economic advantage for fostamatinib, whereas Perplexity AI favored the choice of avatrombopag in the long term in the Spanish context.[5] Recently, an increase in the prescription of avatrombopag has been reported from Norway,[6] since 2022-2023, probably motivated by its efficacy profile and the convenience of oral administration.

Objective

We conducted an analysis of the efficacy and efficiency derived from the use of avatrombopag in different treatment lines, from first line to three or more lines, in the management of patients with ITP at a tertiary-level center.

Method

Data were collected from the patients' electronic health records after prior informed consent had been requested. The variables collected included age, sex, type of ITP (primary/secondary), number of previous treatment lines before starting avatrombopag, the TPO-RAs used before starting avatrombopag, the reason for switching to avatrombopag, platelet count before the switch and at 1, 3, 6, 9, and 12 months, and, finally, the dose of the different agonists at each of these time points. The variation in associated costs at the different time points was analyzed. Results are expressed as mean and SD, median and IQR, and percentage. To calculate the costs of the different treatments, the ex-factory price of the different agonists reported on the following website was used as reference: https://www.farmaceuticos.com/botplus/. Statistical analysis was performed using generative AI (ChatGPT-4o®).

Results

A total of 22 patients were included: 13 women (59.09%) and 9 men (40.91%). The mean age was 55.91 years (SD, 20.9). Overall, 68.18% of patients had a diagnosis of primary ITP. Of the 22 patients, 1 received avatrombopag as first-line therapy, 3 as second-line therapy, and, among the remaining 18 patients, 12 as third-line therapy (54.55%), 2 as fourth-line therapy and 2 as sixth-line therapy (9.09%, respectively), 1 as fifth-line therapy, and another as seventh-line therapy. A total of 45.45% of patients had previously received eltrombopag, another 27.27% had received romiplostim, and 9.09% had received both agonists. Before the switch, 36.36% of patients were receiving concomitant medication for their ITP, preferably prednisone at doses < 5–10 mg/day. The mean dose of romiplostim before the switch (n = 7) was 494.28 mg/week (160–700). The mean dose of eltrombopag before the switch (n = 11) was 450 mg/week (200–525). The mean initial dose of avatrombopag was 165.45 mg/week (140–280), or 140 mg/day if the four patients who started at the maximum dose of 280 mg were excluded: mean platelet count, 16,000/mL (5,000–32,000/mL). The mean dose of avatrombopag at the last follow-up was 143.97 mg/week (7.5–280), or 128.19 mg if the 4 patients who started at the maximum dose were excluded. In the latter patients, the mean final dose was 215 mg/week (20–280). Of these 4 patients, 3 achieved a partial response, according to the 2009 ITP Working Group definition, at the first 1-month follow-up, while patient #4 achieved it at 60 days. If only patients who switched for convenience or who received avatrombopag as first-line therapy in relapse/refractory disease after corticosteroids are considered (12/22), the mean final dose of avatrombopag was 98.33 mg/week (10–280). Statistically significant differences were observed in platelet counts throughout treatment with avatrombopag (ANOVA; p = 0.0018), with a sustained increase in platelet count, from a previous mean of 51,000/mL to ≥ 140,000/mL. Of note, the patient who received avatrombopag as first-line therapy achieved complete remission, which allowed us to discontinue treatment. The weekly treatment cost of the 18 patients treated with agonists before the switch was €12,657.67, corresponding to €703.2/patient/week (Figs. 1 and 2). At 3 months, a reduction in economic cost was already observed: the total weekly cost was €5,886.34, with a mean weekly cost per patient of €280.30. At 12 months, this trend toward cost reduction was consolidated, with a total weekly cost of €5,808.41 and a mean cost per patient/week of €264.02, implying a cost reduction of 54.11% overall and 62.45% per patient, respectively. The difference was statistically significant (Student t test; p < 0.001). In fact, with less than 50% of the previous treatment cost, 4 additional patients were treated, and a reduction in the need for concomitant treatment was observed, decreasing from 8 to 4 patients, although, given the small number of patients, this lacked statistical significance (chi-square test; p = 0.366) (Figs. 1 and 2). When analyzing the effect of switching from eltrombopag to avatrombopag (n = 10), 2 patients who had failed eltrombopag were excluded: 1 patient in the seventh-line therapy and another in the fourth line, both rescued with avatrombopag at the maximum dose (280 mg/week). One of them had received 6 previous lines of treatment, and the other had received 3. The cost of the remaining 8 patients was €6,024/week, which dropped to €4,718/week at the 12-month follow-up, corresponding to a 22% reduction, although an increase in cost was observed with the starting dose within the first month.

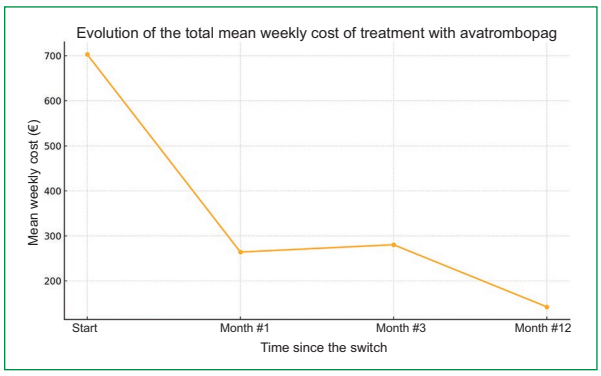


Figure 1. Evolution of the mean weekly cost.

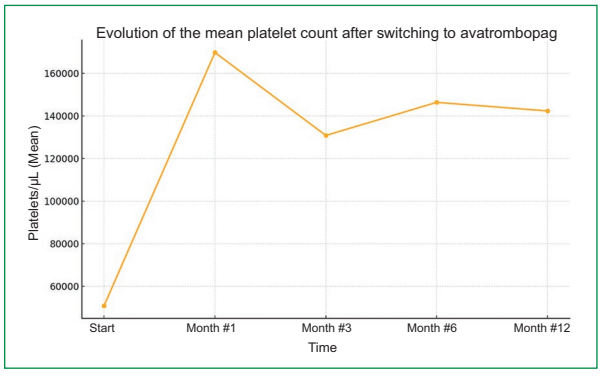


Figure 2. Evolution of the mean platelet count after the switch.

Table 1. Comparison of the different studies

Characteristic	AVESPA study (GEPTI)[3]	NOR-ITP (Norway)[6]	HU *Álvaro Cunqueiro*, EOXI Vigo
Design	Multicenter retrospective	Multicenter retrospective/ prospective	Retrospective, single-center
Total sample	268 patients with ITP treated with Ava	87 patients with ITP; 14 treated with Ava	22 patients treated with Ava
Mean age	59 years	60 years	55.9 years
% women	58.0%	50.0%	59.0%
Start of Ava use	2022–2024	Increasing use in 2022–2023	Since late 2023
First-line Ava	Very low (1.1%)	16% of TPO-RAs used in the "new" ITP phase	1 patient (4.5%)
Use after other TPO-RAs	Yes; eltrombopag and romiplostim, even in combination	Yes	81.8% had used eltrombopag and/or romiplostim
Overall response rate	92% achieved ≥ 50 × 109/L	100% for Ava (14/14)	Significant improvement, from 51,000 to > 140,000/μL; P = 0.0018
SROT (sustained response off treatment)	Not evaluated	6% with eltrombopag, 9% with romiplostim; not reported for Ava	1 patient discontinued treatment after complete remission
Discontinuation due to remission	Not clearly detailed	29% with Ava, 30-36% with other TPO-RAs	1 case with complete remission
Time to response, median	13 days (IQR, 7-21)	7 days with Ava, 10 days with eltrombopag	Not detailed
Concomitant treatment	Reduction in 80% of patients receiving corticosteroids	Not analyzed in detail	Reduced in 4 of 8 patients; not significant
Safety (AEs)	Thrombocytosis (15%), VTE (4.5%), non-serious AEs in 17%	AEs in 25%; thrombosis 2%, fibrosis 2%	No serious AEs reported
Costs	Not evaluated	Not evaluated	54.1% reduction in total cost and 62.45% reduction per patient
Main clinical relevance	High efficacy in refractory cases and corticosteroid reduction	Increased prescription of Ava as the first option in second-line treatment since 2022-2023	High efficacy, lower variability, and substantial economic efficiency

AEs: adverse events; Ava: avatrombopag; GEPTI: *Grupo Español de Púrpura Trombocitopénica Idiopática*; IQR: interquartile range; ITP: idiopathic thrombocytopenic purpura; TPO-RA: thrombopoietin receptor agonist; VTE: venous thromboembolism.

Discussion

Despite the small size of our series, the results are highly elucidative. In addition to the advantages observed from a clinical standpoint, with an increase in the mean platelet count (Fig. 3) compared with previous treatments, a considerable reduction is observed in the economic cost associated with the use of agonists, increasing the number of patients who could potentially be treated with the same budget. Similarly, a trend toward dose reduction over time was observed both in patients who started at the standard dose (140 mg/day, 9% reduction) as well as in those who started at the maximum dose (280 mg/day, 23% reduction). We observed that the dose reduction was more marked in patients who started avatrombopag for convenience or as first-line therapy in early relapse/refractoriness (30% reduction), compared with those who received it after multiple lines or because of loss of response. This finding could be explained by greater therapeutic sensitivity in less advanced stages of the disease and lower prior exposure to immunosuppressants or other agonists, which would make it possible to achieve therapeutic goals with lower dose requirements. These findings are consistent with the results of the Spanish real-world study.[3] In that study, although mean doses after the switch were not reported, which prevents an estimate

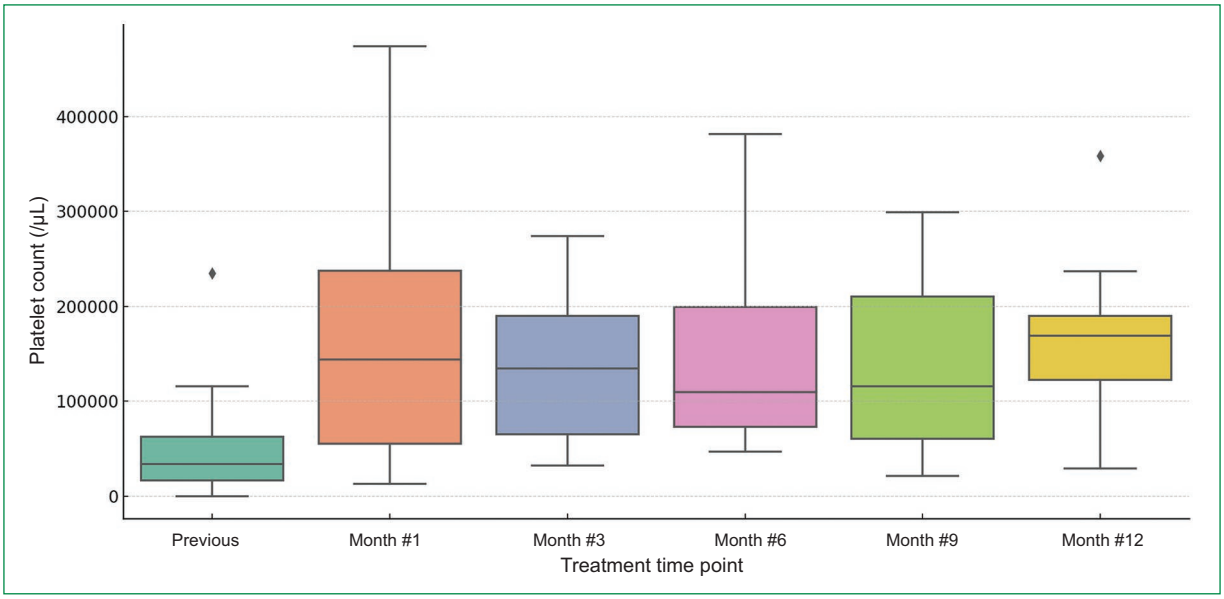


Figure 3. Distribution of platelet count at different time points during treatment with avatrombopag. The median, shown as the line inside each box, increases over time, suggesting sustained improvement. The dispersion of values, reflected by the wide IQR, indicates variability in response among patients, especially during the first months.

of the efficiency of the change, it is stated that most patients who remained on avatrombopag were using < 140 mg/week at the end of the study, without specifying an exact mean range or detailing the specific regimens within that category. In total, 23 patients started avatrombopag for reasons other than therapeutic failure; 95.7% of them achieved response, and 62% were using doses ≤ 140 mg/week. Of these 23 patients, only 10 had previously received one or both agonists (romiplostim/eltrombopag). These results are also consistent with the findings of the prospective study by Tarantino et al.,[7] which specifically evaluated 44 adult patients with ITP who switched from eltrombopag or romiplostim to avatrombopag, maintaining an adequate platelet response without a washout period. In addition to stability in platelet counts, a significant improvement was observed in treatment satisfaction, especially in the domains of convenience and efficacy, measured using the TSQM (Treatment Satisfaction Questionnaire for Medication). The absence of thrombotic events, the low incidence rate of serious adverse events, and the positive patient perception reinforce the favorable profile of avatrombopag in clinical settings where the aim is to improve tolerability or adherence, an aspect also reflected in our series. The clinical validity of the therapeutic switch, even in patients who responded to previous treatments, allows the switch to be considered not only as a solution in the event of therapeutic failure, but also as a proactive strategy to optimize treatment convenience, safety, or efficiency.

The report by Tomasello[6] does not report mean dose, but it does indicate that avatrombopag and romiplostim show a faster response in terms of median time, 7 days, compared with eltrombopag, 10 days, and also that variability, measured by IQR width, is similar among the three agents. As in AVESPA,[3] it is indicated that, with avatrombopag, probably because of the shorter follow-up time, it is not possible to determine SROT, defined as sustained response off treatment and discontinuation rates. Nor is it possible to perform a cost-efficiency analysis with the reported data, but the results reinforce the growing and effective use of avatrombopag as a first- or second-line option because of its high initial response rate and complete response rate, 100% vs. 61% with romiplostim and 56% with eltrombopag. Regarding the use of avatrombopag as first-line therapy, the AVESPA study reports 1.1% of the total number of patients; in our case, one patient (4.5%) also achieved complete remission. AVESPA reports that 80% of patients reduced or discontinued concomitant treatment, whereas this percentage in our series is 50%; however, there appears to be a positive trend in this regard, which was not explicitly assessed in the Norwegian series (Table 1). Obviously, this reduction or discontinuation is associated with a reduction in the economic cost of treatment in these patients. A study by Cooper et al.[8]

was recently published evaluating the cost-effectiveness of avatrombopag compared with eltrombopag and romiplostim as second-line treatment for adults with ITP in the United Kingdom, using a Markov model with a lifetime time horizon to estimate clinical and economic outcomes from the perspective of the National Health Service (NHS). Their evaluation considered aspects related to clinical efficacy as well as clinically relevant events, such as bleeding, concomitant treatments, and treatment-related adverse effects. The ICER, incremental cost-effectiveness ratio, compared with romiplostim shows that avatrombopag is dominant, that is, more effective and less costly. Compared with eltrombopag, the ICER is £5,982/QALY, quality-adjusted life-year, which is very favorable from the perspective of the United Kingdom health system, where a treatment is usually considered cost-effective if its ICER is below the threshold of £20,000-£30,000 per QALY. This analysis by Cooper supports the use of avatrombopag as a cost-effective second-line treatment for ITP in adults, with clear advantages over romiplostim and a favorable cost-effectiveness ratio compared with eltrombopag. Although methodological limitations require caution, the results are robust and may help guide clinical and health policy decision-making. Of note, the ICER in Spain is similar to that considered in the United Kingdom. In this regard, despite the lack of direct data on quality-adjusted life-years (QALYs), a simulation can be performed, using generative AI, of the ICER using the response rate from the AVESPA study[3] (92.2%) as the effectiveness estimator. This was compared with a mean historical response rate of 65% for other TPO-RAs, such as eltrombopag and romiplostim. Applying the annual costs before and after the switch to avatrombopag at our center (€36,566.4 vs. €13,729 per patient), the calculated ICER was –€83,953/QALY, which would indicate that avatrombopag is a dominant alternative, that is, more effective and less costly. Although preliminary, this simulation reinforces the favorable clinical and economic impact observed in our local experience.

Conclusions

In our experience, the switch to avatrombopag has been successful both clinically, because of its high efficacy, improving platelet counts with lower variability, and in terms of efficiency, because of the substantial reduction in ITP treatment costs (54.1%), allowing more patients to be treated at half the cost, with a 62.45% reduction in weekly cost per patient. It would be important to conduct a multivariate analysis, but the small sample size limits this type of analysis, as well as the ability to determine whether the reduction in concomitant treatment has statistical significance. The reduction of concomitant treatment in 50% of patients would be supported by observations reported in other real-world studies in our setting. The reduction in total weekly cost and per-patient cost at 12 months is highly statistically significant and highlights the favorable economic impact of switching to the "new" agonist. In our opinion, these data raise serious doubts about the suitability of widespread use of future generic formulations of eltrombopag, in which, beyond cost, no advantage over avatrombopag can be discerned. Avatrombopag, as a second-generation agonist, has succeeded in overcoming the shortcomings of eltrombopag, a first-generation oral agonist, such as interference with food and the need for liver monitoring. These shortcomings will not be overcome by generic eltrombopag. The results of the AVESPA study[3] already provided robust evidence on the use of avatrombopag in clinical practice, supporting its inclusion as a second-line, or even first-line, alternative in the management of ITP. Its results support its use in refractory patients and in contexts where the aim is to minimize immunosuppression or reduce bleeding risk, with high efficacy even in complex subgroups and a very acceptable safety profile. For example, it presents an incidence of thromboembolic events as low as 4%. In fact, different authors[9,10] state that avatrombopag, compared with other TPO-RAs, seems to be the optimal option as second-line treatment for ITP in adults, since it provides the greatest short-term benefit as second-line treatment while awaiting demonstration of its ability to achieve complete remissions and discontinuation rates. The results of the British cost-effectiveness analysis[8] are reinforced by the clinical evidence from the AVESPA study[3] and the Norwegian registry,[6] which highlight the efficacy, safety, and favorable profile of avatrombopag in real-world practice, although only the Norwegian study includes an analysis of the discontinuation rate. These findings would be complemented by local analyses such as that from our center, which demonstrates its direct budgetary impact, with a significant reduction in spending on TPO-RAs without compromising efficacy, with the limitation of the small sample size. Pending a cost-effectiveness analysis in our setting, it seems clear that the convergence of the different results would support consideration of avatrombopag as the preferred agonist in clinical decision-making, first choice within second-line

treatment for ITP, and in health policies, similarly to what occurs in neighboring countries such as Norway.

Funding

None.

Conflicts of interest

The author declares having participated in meetings and advisory boards for Octapharma, Novo Nordisk, CSL Behring, Sobi, and Amgen.

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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ORIGINAL ARTICLE

Prophylaxis in patients with moderate and mild haemophilia: experience from a single centre

Profilaxis en pacientes con formas moderadas-leves de hemofilia: experiencia desde un hospital individual

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Abstract

Introduction: *Prophylaxis in hemophilia as a gold standard of treatment was classically restricted to patients with severe forms.* **Objective:** *To evaluate the implementation of prophylaxis in patients with moderate and mild hemophilia, addressing its impact on the reduction of bleeding and quality of life.* **Material and methods:** *Nine patients were included, analyzing retrospective data 12 months before and after starting prophylaxis collected from their electronic medical records.* **Results:** *It's observed a significant reduction in annualized bleeding rate by 96.78% for hemophilia A and 91.67% for hemophilia B. Concentrates of factors VIII and IX were used with different infusion regimens. Prophylaxis improved hospital independence and decreased joint bleeding, although with a burden associated with treatment.* **Conclusions:** *The need for early follow-up and adoption of prophylaxis in non-severe patients to prevent arthropathies and improve quality of life is highlighted, in line with international recommendations.*

Keywords: *Prophylaxis. Non-severe hemophilia. Annualized bleeding rate (ABR). Quality of life.*

Resumen

Introducción: *La profilaxis en la hemofilia como método preferido de tratamiento se restringía clásicamente a los pacientes con formas graves.* **Objetivo:** *Evaluar la implementación de profilaxis en pacientes con hemofilia moderada y leve, abordando su impacto en la reducción de sangrados y en calidad de vida.* **Material y métodos:** *Incluye nueve pacientes, analizando datos retrospectivos 12 meses antes y después de iniciar la profilaxis, datos recogidos de sus historias clínicas electrónicas.* **Resultados:** *Se observa una reducción significativa de la tasa anualizada de sangrado en un 96,78% para hemofilia A y un 91,67% para hemofilia B. Se emplearon concentrados de factores VIII y IX con distintos regímenes de infusión. La profilaxis mejoró la independencia hospitalaria y disminuyó los sangrados articulares, aunque con una carga asociada al tratamiento.* **Conclusiones:** *Se destaca la necesidad de un seguimiento temprano y adopción de la profilaxis en pacientes no graves para prevenir artropatías y mejorar la calidad de vida, alineándose con recomendaciones internacionales.*

Palabras clave: *Profilaxis. Hemofilia no grave. Tasa anualizada de sangrado (TAS). Calidad de vida.*

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Date of reception: 07-12-2024
Date of acceptance: 28-07-2025
DOI: 10.24875/RHT.M25000077

Available online: 03-09-2026
Hemost Trombos (Eng). 2026;3(2):51-55
www.revistahemostasiaytrombosis.com

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Introduction

Hemophilia A and B are X-linked recessive disorders caused by deficiencies of factor VIII (FVIII) and factor IX (FIX), respectively. Clinically, they are characterized by spontaneous or trauma-related bleeding, the severity of which is associated with the residual plasma activity of the deficient protein.[1] Three severity categories are distinguished: severe (< 1 IU/dL), moderate (1–5 IU/dL), and mild (5–40 IU/dL). Moderate forms are the least common in hemophilia A (HA),[2] whereas in hemophilia B (HB), the frequency is similar across the different severity categories (33%). According to the latest World Federation of Hemophilia guidelines, prophylaxis should be offered to patients with HA or HB and a severe phenotype. This recommendation includes some patients with moderate hemophilia and a clinically severe phenotype,[3] and is supported by the findings of several real-world studies.[4-6] The latest British clinical practice guidelines[7] recommend considering prophylaxis for all children with baseline FVIII levels of 1–3 IU/dL. They also recommend offering prophylaxis to any patient with hemophilia who experiences 1 or more spontaneous hemarthroses or who has established joint damage caused by recurrent hemarthroses with ongoing bleeding.

These recommendations are entirely reasonable, considering that "2 or 3 bleeding episodes in the same joint may cause progressive and irreversible damage"[8] and that "the severity of joint impairment is the main factor affecting the quality of life of our patients."[9] We report our center's experience with the implementation of prophylaxis in a group of patients with moderate or mild hemophilia who agreed to begin this treatment modality and describe its impact on quality of life, both in terms of reduced bleeding and decreased dependence on hospital care.

Objective

To evaluate the impact of prophylaxis with FVIII or FIX concentrates on the health and quality of life of patients with moderate or mild hemophilia A or B treated at a tertiary care center.

Methods

We conducted a retrospective analysis of clinical data from patients with moderate or mild hemophilia who received prophylaxis with factor concentrates. Data were obtained from the electronic health record for the 12 months before and the 12 months after prophylaxis initiation. The following variables were collected: type of hemophilia; factor level measured using a 1-stage clotting assay; annualized bleeding rate before and after prophylaxis; prophylactic infusion frequency; weekly factor consumption per kilogram of body weight; trough level; presence or absence of arthropathy; and type of prophylaxis, classified as primary, secondary, or tertiary. Quality of life was assessed using the EQ-5D questionnaire (European Quality of Life-5 Dimensions). The analysis was descriptive. Qualitative variables were expressed as absolute values, percentages, and confidence intervals, whereas quantitative variables were expressed as means and SDs.

Results

Nine patients were analyzed: 5 with moderate HA, 4 with moderate HB, and 1 with mild HB. Three patients with HA were children or adolescents. The mean age of the adult patients was 46.8 years (range, 35–73 years). Among all patients at the center with moderate hemophilia and FVIII or FIX levels of 2–5 IU/dL who had previously received on-demand treatment, 75% began prophylaxis with factor concentrates. Six patients were initially included, although the analysis was ultimately conducted in 5 patients with HA. Their mean FVIII activity measured using a clotting assay was 3.4 IU/dL. Mean factor consumption was 105 IU/kg/wk for standard half-life FVIII concentrate, administered 3 times weekly, and 90 IU/kg/wk for extended half-life FVIII concentrate, administered twice weekly. One patient initially began prophylaxis with extended half-life FVIII concentrate once weekly but requested a change to twice-weekly administration because the patient felt safer with the more frequent regimen. Prophylaxis was adjusted to achieve a minimum factor level of 5 IU/dL. The total annualized bleeding rate decreased by 96.78%, from a mean of 6.2 before prophylaxis to 0.2 after prophylaxis. No emergency department visits for bleeding were recorded after prophylaxis initiation. One patient experienced traumatic hemarthrosis of the left ankle that required treatment with 2 additional doses of extended half-life FVIII concentrate, self-administered at home.

A total of 75% of patients with nonsevere HB were receiving prophylaxis: 4 patients with moderate HB, with a mean FIX level of 3.3 IU/dL, and 1 patient with mild HB, with a FIX level of 6 IU/dL. All had established arthropathy of varying severity and at different anatomical sites, most commonly affecting the left ankle. All patients except 1 received prophylaxis with extended half-life FIX concentrate once weekly at a dose of 60 IU/

Table 1. Baseline characteristics, prophylaxis regimen, and changes in annualized bleeding rate in the 9 included patients

Factor level	Preprophylaxis ABR	Preprophylaxis ED visits	Prophylaxis frequency	Factor concentrate	Trough level	Postprophylaxis ABR	Postprophylaxis ED visits	Arthropathy	Type of prophylaxis
3.8 IU/dL	13	13	3 times/wk	SHL, 105 IU/kg/wk	> 5 IU/dL	1	0	No	Primary
3.2 IU/dL	9	9	3 times/wk	SHL, 105 IU/kg/wk	4–5 IU/dL	0	0	No	Primary
3.8 IU/dL	2	1	3 times/wk	SHL, 105 IU/kg/wk	5–6 IU/dL	0	0	No	Primary
4 IU/dL	4	2	2 times/wk	EHL, 90 IU/kg/wk	5–6 IU/dL	0	0	Yes (left ankle)	Tertiary
3.2 IU/dL	3	2	2 times/wk	EHL, 90 IU/kg/wk	4–5 IU/dL	0	0	Yes (right elbow)	Tertiary
3.5 IU/dL	4	4	Once weekly	EHL, 60 IU/kg/wk	5–6 IU/dL	1	0	Yes (left ankle and left elbow)	Tertiary
3 IU/dL	4	4	Once weekly	EHL, 60 IU/kg/wk	5–6 IU/dL	0	0	Yes (left ankle and hip)	Tertiary
6 IU/dL	2	0	Once weekly	EHL, 60 IU/kg/wk	> 6 IU/dL	0	0	Yes (left ankle)	Tertiary
3.5 IU/dL	2	2	Once weekly	SHL, 100 IU/kg/wk	NA	0	0	Yes (knees)	Tertiary

ABR: annualized bleeding rate; ED: emergency department; EHL: extended half-life factor concentrate; NA: not available; OSA: one-stage clotting assay; SHL: standard half-life factor concentrate; wk: week.

kg. The total annualized bleeding rate decreased by 91.67%, from a mean of 3 before prophylaxis to 0.25 after prophylaxis. None of these patients required emergency department care for bleeding. One patient receiving weekly prophylaxis with 100 IU/kg of a standard half-life FIX concentrate experienced traumatic hemarthrosis of the right knee, requiring 3 additional doses of standard half-life FIX concentrate until resolution. Treatment was administered in the Day Hospital at our center (Table 1). Regarding the EQ-5D-5L, the mean index value was 0.8, indicating the presence of some problems in at least 1 dimension but an overall relatively favorable health status within the range of 0.8–1. The reported problems were generally mild to moderate and were mainly related to mobility. The mean visual analog scale score was 90.

Discussion

Several studies have shown that patients with mild or moderate hemophilia may also develop joint lesions and are at risk of requiring orthopedic surgery because of joint bleeding. Therefore, according to current guidelines, identifying candidates for prophylaxis and implementing this strategy in this patient group are important, particularly among individuals with more severe bleeding phenotypes. A recent publication by the group at *Hospital Universitario La Paz* (Madrid, Spain) evaluated risk factors associated with arthropathy in 85 patients with mild HA.[6] The investigators analyzed several variables in relation to the presence or absence of joint damage and the severity of arthropathy. Two variables were independently associated with arthropathy: age, with a median of 42 years, and plasma factor activity, with a median of 10.5 IU/dL. The investigators estimated that the risk of arthropathy increased by 7.9% for each additional year of life and decreased by 7.7% for each 1-IU/dL increase in baseline factor activity. Furthermore, once arthropathy developed, its severity could be influenced by the patient's level of physical activity. In our series, the 3 patients receiving primary prophylaxis comprised 2 children and 1 adolescent younger than 18 years who engaged in intensive physical activity. This further supported the implementation of prophylaxis as a treatment strategy. The remaining patients were adults with established joint damage.

The observations reported by the group at *Hospital Universitario La Paz* are consistent with previous findings, including those reported by Wang et al.[10] and Collins,[11] who found that the main variable associated with loss of joint range of motion in patients with hemophilia was the plasma factor level, particularly when levels were < 10 IU/dL. The MoHem study,[5] which evaluated the prevalence of arthropathy in 145 Nordic patients with moderate HA or HB and a median age of 28 years, concluded that current joint health in these patients was generally favorable. However, the investigators identified a subgroup with severe arthropathy. FVIII: C or FIX levels of 3 IU/dL or lower and moderate HA were associated with a more severe bleeding phenotype. The authors therefore suggested primary prophylaxis for patients with FVIII or FIX levels of < 3 IU/dL. Furthermore, they stated that a key factor in joint deterioration was the interval between the first bleeding episode and the age at prophylaxis initiation, with a median interval of 10 years. In addition, when these patients were compared with a Swedish cohort of patients with severe HA receiving prophylaxis, patients with moderate hemophilia reached a Hemophilia Joint Health Score > 10 in half the time required by patients with severe disease. This finding reinforces the observation made by Collins[11] regarding the difference in protection against bleeding between, for example, a baseline level of 2 IU/dL in a patient with moderate hemophilia and a trough level of 2% in a patient with severe hemophilia receiving prophylaxis with factor concentrates. In our study, baseline FVIII and FIX levels were slightly higher, at 3.4 and 3.3 IU/dL, respectively. However, 100% of the patients had a history of hemarthrosis, compared with 85% and 73%, respectively, in the MoHem study.

A Dutch study[12] evaluated joint status using magnetic resonance imaging in 51 patients with nonsevere HA, 63% of whom had mild HA and 37% moderate HA, together with the Hemophilia Joint Health Score. The mean FVIII: C level was 10 IU/dL (IQR, 4–16 IU/dL), and the mean age was 43 years. The median Hemophilia Joint Health Score was higher in patients with moderate HA than in those with mild HA, at 7 vs 4. Of note, hemosiderin deposits were found in 14% of joints among patients who had never experienced clinically apparent joint bleeding. This finding may reflect microbleeding or subclinical bleeding and indicates that greater attention should be paid to the joint health of patients with nonsevere hemophilia. Indeed, in the PROBE study,[4] 82.8% of patients with moderate hemophilia receiving on-demand treatment experienced more than 2–3 bleeding episodes per year.

In our series, prophylaxis was effective in reducing the annualized bleeding rate and the associated disease burden, despite requiring regular infusion of factor concentrates and therefore increasing treatment burden. Currently, no treatment alternatives are available for nonsevere HB beyond intravenous FIX replacement. In HA, however, subcutaneous prophylaxis with emicizumab represents an alternative.[13] Nevertheless, in patients with moderate HA, defined by FVIII: C levels of 1–5 IU/dL, its use is generally considered in those with a clinically severe bleeding phenotype. In theory, this requirement represents a barrier to the use of emicizumab in primary prophylaxis programs because of the difficulty of predicting the bleeding phenotype using the score proposed by the subcommittees of the International Society on Thrombosis and Haemostasis.[14] This limitation exists despite the favorable findings reported in the HAVEN 6 clinical trial.[15]

Álvarez Román et al.[16] suggested that joint damage is not adequately prevented in patients with nonsevere hemophilia. In our series, and overall, patients reported satisfaction with the effect of prophylaxis on their quality of life. Only 1 patient discontinued treatment because of the associated treatment burden. The benefits reported by patients were attributable not only to the reduction in bleeding but also to the decreased need for hospital care and the disappearance of joint pain. Patients were progressively able to increase their physical activity safely because of the additional protection provided by regular factor infusion. Because age and residual plasma factor activity should be considered when estimating the risk of bleeding and, consequently, arthropathy in this patient group, continued follow-up of patients with nonsevere hemophilia in specialized clinics is important.[17] Furthermore, it may be appropriate to consider implementing primary or secondary prophylaxis programs beginning in childhood. Although prophylaxis has not traditionally been considered mandatory for patients with moderate hemophilia, the latest Spanish registry[17] showed that only 26.4% of patients with moderate HA and 24% of those with moderate HB were receiving prophylaxis. Nevertheless, its implementation is likely to become increasingly widespread as further studies confirm the current findings.

Our study has several limitations. First, the small sample size does not allow definitive conclusions to be drawn, particularly regarding the implementation of a treatment strategy associated with high economic costs. Second, it would have been useful to evaluate joint status using the Hemophilia Early Arthropathy Detection With Ultrasound protocol before prophylaxis initiation and again 12 months later. This would have allowed comparison of the findings and objective assessment of

the clinical benefit of prophylaxis beyond the reduction in the annualized bleeding rate. Similarly, quality of life, assessed using the EQ-5D-5L, was evaluated only at the end of the study and not before prophylaxis initiation, which also limits interpretation of this outcome.

Conclusions

In our opinion, prophylaxis should be implemented as the standard of care for patients with moderate or mild hemophilia and a bleeding phenotype to prevent joint complications and improve quality of life. The substantial reduction in the annualized bleeding rate observed among patients with both HA and HB supports this therapeutic approach. In addition to the benefit associated with reducing bleeding frequency, a decrease in the need for hospital visits and an overall improvement in patients' perceptions of their health status were observed.

Although prophylaxis requires a substantial commitment because of the need for regular infusions, its benefits outweigh these barriers, particularly in terms of reduced joint pain and a greater ability to engage safely in physical activity. This series highlights that early implementation of prophylaxis, even in patients with nonsevere hemophilia, may prevent the development of joint complications and reduce the long-term disease burden. Nevertheless, these findings require confirmation in future studies.

Finally, although prophylaxis in nonsevere hemophilia is not currently universally adopted, its use is likely to become more widespread as additional scientific evidence regarding its effectiveness accumulates.

Funding

None declared.

Conflicts of interest

None declared.

Ethical considerations

Protection of human participants and animals. The authors declare that no experiments involving humans or animals were conducted specifically for this study.

Confidentiality, informed consent, and ethical approval. The authors obtained approval from the Ethics Committee for the analysis of routinely collected, anonymized clinical data; therefore, informed consent was not required. The relevant ethical recommendations were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence tools were used in the preparation of this manuscript.

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ORIGINAL RESEARCH ARTICLE

Inhibitors in non-severe hemophilia A: a case report

Inhibidores en hemofilia A no grave: a propósito de un caso

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Abstract

Introduction: *The development of inhibitory antibodies against factor VIII (FVIII) is a complication in approximately 30% of patients with severe hemophilia A, increasing bleeding frequency and resistance to treatment.* **Objective:** *To report the experience of a tertiary care center in the management of an inhibitor or neutralizing antibody against FVIII in a patient with mild hemophilia A and to provide a brief critical review of the topic.* **Material and methods:** *The identified mutation was c.6301 C > G in exon 22 of the F8 gene, not among the missense variants previously associated with the highest inhibitor risk. In the absence of DDAVP response, the acute bleeding episode was managed with recombinant factor VIIa, and immunosuppression with prednisone was initiated. On day 7, as the inhibitor titre rose to 17 BU, rituximab (anti-CD20) was added at the standard dose of 375 mg/m² weekly for four weeks.* **Results:** *The inhibitor became undetectable at 2.5 months, and baseline FVIII: C levels were restored at 3.5 months, with a positive DDAVP challenge. At 12 months, the patient remains in complete remission.* **Conclusions:** *This case highlights the heterogeneity in managing inhibitors in non-severe haemophilia A, the lack of standardised guidelines, and the need for an individualised therapeutic approach. The complementary role of emicizumab is discussed, along with modifiable risk factors — FVIII dose, treatment duration, and surgical exposure — for inhibitor prevention.*

Keywords: *Non-severe Haemophilia A. Inhibitors AntiFVIII. Immunosuppression. Erradication.*

Resumen

Introducción: *El desarrollo de anticuerpos inhibidores frente al factor VIII (F8) es una complicación en cerca del 30% de los pacientes con hemofilia A grave, aumentando la frecuencia de sangrados y la resistencia al tratamiento.* **Objetivo:** *Reportar la experiencia en el manejo de un inhibidor o anticuerpo neutralizante frente al F8 en un paciente con hemofilia A leve en un centro de tercer nivel y hacer una breve revisión crítica del tema.* **Material y métodos:** *La mutación identificada fue c.6301 C > G en el exón 22 del gen F8, sin correspondencia con las variantes missense de mayor riesgo conocidas. Ante la ausencia de respuesta a desmopresina, se trató el episodio hemorrágico con factor VIIa recombinante y se inició inmunosupresión con prednisona. Al séptimo día, ante la elevación del título a 17 UB, se añadió rituximab (anti-CD20) en pauta estándar de 4 dosis semanales.* **Resultados:** *El inhibidor se negativizó a los 2,5 meses y el FVIII: C recuperó valores basales a los 3,5 meses, con respuesta positiva al test de DDAVP. A los 12 meses el paciente permanece en remisión completa.* **Conclusiones:** *El caso ilustra la heterogeneidad en el manejo de los inhibidores en hemofilia A no grave, la ausencia de guías estandarizadas y la necesidad de individualizar la estrategia terapéutica. Se discute el papel complementario del emicizumab y se destacan los factores de riesgo modificables (dosis de FVIII, duración del tratamiento, tipo de cirugía) para prevenir esta complicación.*

Palabras clave: *Hemofilia A no grave. Inhibidor AntiF8. Inmunosupresion. Erradicacion.*

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Date of reception: 11-11-2024
Date of acceptance: 28-03-2025
DOI: 10.24875/RHT.M25000075

Available online: 03-09-2026
Hemost Trombos (Eng). 2026;3(2):56-60
www.revistahemostasiaytrombosis.com

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Introduction

The development of inhibitory antibodies against factor VIII (FVIII) is a complication in approximately 30% of patients with severe hemophilia A, increasing bleeding frequency and resistance to treatment. In mild hemophilia A (FVIII:C > 5%), desmopressin (DDAVP, 1-deamino-8-D-arginine vasopressin) is the first-line therapy.[1] This depends on response, bleeding severity, and treatment duration.[1,2] If DDAVP fails, which occurs in 40%–50% of cases, FVIII concentrates (FVIIIC) are the treatment of choice. The incidence rate of inhibitors in these patients is variable (3%–13%), but certain FVIII genotypes are associated with higher rates.[3,4] Eckhardt et al.[4] identified, among the 250–300 missense mutations described, 19 particularly high-risk mutations located in the A2 domain of the heavy chain and in the A3, C1, and C2 domains of the FVIII light chain, some with a risk of inhibitor development > 20%–40%. In addition, the risk remains elevated throughout life and, unlike in severe hemophilia A, does not decrease after the first 50 exposure days (> 50 exposure days [ED]).[5]

The aim of the present study was to report the experience of a tertiary care center in the management of an inhibitor or neutralizing antibody against FVIII in a patient with mild hemophilia A and to provide a brief critical review of the topic.

Method

We describe the case report of a patient with mild hemophilia A who developed a high-titer inhibitor (> 5 Bethesda units [BU]) after intensive treatment for an apparently spontaneous dorsal spinal hematoma. The strategy used for inhibitor eradication is described.

Description and results

The patient was a 20-year-old man diagnosed with mild hemophilia A (FVIII:C 14%, chromogenic FVIII 12%) with no inhibitor at 13 years of age, in the context of a rupture of the right lateral meniscus and secondary traumatic hemarthrosis of the right knee. At that time, he had no known family history of hemophilia, but genetic testing performed subsequently showed a c.6301 C > G mutation, according to the NM_000132.3 reference sequence, in exon 22 of the FVIII gene. He received intensive treatment with recombinant FVIII concentrate (moroctocog alfa) for 6 days, completed treatment with DDAVP, and began secondary prophylaxis for 4 weeks with alternating moroctocog alfa and DDAVP, 3 days per week, until completion of physiotherapy. FVIII inhibitor screening at 30 and 60 days was negative (< 0.4 BU). He received occasional care for dental procedures, which were managed with DDAVP and tranexamic acid. Five years later, he presented to the emergency department of our center with a 3-week history of central, radiating back pain of progressive onset, with no apparent relationship to any activity. Computed tomography showed an image compatible with a dorsal epidural spinal hematoma. Hospital admission was decided, and intensive treatment with moroctocog alfa was started for 2 weeks, followed by prophylaxis alternating moroctocog alfa and DDAVP until completing 1 month of treatment. At the first post-treatment assessment, 1 month later, the anti-FVIII inhibitor tested negative (< 0.4 BU). Three weeks later, he again presented to the emergency department with spontaneous pain in the right iliac fossa radiating to the testicle. Abdominal ultrasound showed a 2 × 3-cm perireteral hematoma. The spontaneous development of the hematoma, together with the recent intensive treatment, alerted us to the possible development of an inhibitory antibody. The Bethesda assay was performed and showed the presence of a high-titer antibody against FVIII (12.8 BU) (FVIII:C 5.6%), an adverse event that has already been reported to the *Agencia Española de Medicamentos y Productos Sanitarios*. Given the absence of response to DDAVP, treatment with recombinant activated factor VII (rFVIIa) was started, with a good response and resolution of the clinical picture in approximately 7 days. Simultaneously, immunosuppressive treatment with corticosteroids (prednisone, 1 mg/kg per day) was started. Seven days later, because of the increase in antibody titer (17 BU), an anti-CD20 monoclonal antibody was added at the usual dose (375 mg/m^2 weekly for 4 weeks). After 14 days, corticosteroid therapy was tapered over approximately 2 months, maintaining a dose of 5 mg for 2 additional weeks and then 5 mg every other day for another 2 weeks, until completing 3 months of immunosuppressive therapy. The inhibitor titer gradually decreased (Table 1) until becoming negative 2.5 months after the start of immunosuppression. FVIII:C levels reached the patient's normal value at 3.5 months, at which time the DDAVP test was repeated and showed response (FVIII:C > 50% at 4 hours). A pharmacokinetic study was performed using WAPPS-Hemo after administration of a 40 IU/kg dose of combined von Willebrand factor and factor VIII (Fanhdi®). The results confirmed treatment success (recovery, 82%; terminal half-life, 9 hours). Currently, more than 12 months later, he remains in complete

Table 1. Treatment and course of the inhibitor

Days	Inhibitor titer	Treatment	Additional treatment
Day 1	12.8 BU	PDN 1 mg/kg/day	
Day 7	17 BU	PDN 1 mg/kg/day	Anti-CD20 375 mg/m^2/week
Day 14	13 BU	Progressive PDN tapering started	2nd anti-CD20 dose
Day 21	10 BU		3rd anti-CD20 dose
Day 28	5.6 BU		4th anti-CD20 dose
Day 35	4 BU	Continued PDN tapering	
Day 75	< 0.4 BU	PDN 5 mg every other day	
Day 90	< 0.4 BU	PDN discontinued	
Day 105	< 0.4 BU; FVIII 14.6%; DDAVP response test: responder		

DDAVP: desmopressin; PDN: prednisone; S/D: solvent/detergent.

remission and has only required treatment for a mild traumatic hematoma in the right biceps brachii, which resolved with DDAVP and antifibrinolytics.

Discussion

Unlike inhibitors in severe forms of hemophilia A, patients with mild or moderate forms who develop a neutralizing antibody face the absence of guidelines standardizing the management of this complication, as well as substantial heterogeneity in the recommendations reported in the scientific literature. This is a serious problem with a very negative impact on all aspects of the patient's life, from clinical status to psychological well-being. The bleeding phenotype is up to 10 times more severe than that of patients without inhibitors, with an annual bleeding rate of 1.1 (IQR, 0.1–2.5).[6] It often resembles the hemorrhagic phenotype of patients with acquired hemophilia A (40%).[6] The intensity of treatment received,[1,3,7] as well as treatment duration longer than 10 days, influences the risk of developing an inhibitor in these patients. Our patient received treatment for almost 10 days, with FVIII concentrate doses > 40–45 IU/kg per day. Regarding the mutation,[4] some mutations are associated with a higher risk of inhibitor development. The mutation present in our patient has been reported in 3 cases in the database of the European Association for Haemophilia and Allied Disorders (https://dbs.eahad.org/; accessed November 9, 2024). It is a missense mutation that entails an amino acid change (p.[His2101Asp]), although it does not correspond to any of the missense mutations associated with a higher risk of inhibitor development, such as Trp2229Cys (risk, 41.7%) or Asp2074Gly (risk, 21.25%). Regarding the eradication strategy, there are no clinical practice guidelines on its exact management.[1] Experience is limited and ranges from simple observation to immune tolerance induction strategies similar to those used in patients with severe congenital hemophilia A, as well as immunosuppression, similar to that used in the management of acquired hemophilia. Emicizumab is indicated for bleeding prophylaxis in these patients and has shown efficacy both in clinical trials[8] and in real-world practice[9]; therefore, it may complement any of the previously mentioned approaches. The literature includes reports on the outcomes of the different strategies. The INSIGHT Study Group[3] included 101 patients with nonsevere hemophilia A (FVIII:C, 2%–40%) and a median age of 37 years (IQR, 15–60). The median maximum inhibitor titer was 7 BU (IQR, 2–30). Spontaneous disappearance of the inhibitor occurred in 51 of 73 patients, whereas success was achieved in 21 of 28 patients who underwent an eradication strategy. Overall, 64% of patients in whom the antibody became negative remained antibody-free after reexposure to FVIII concentrate. Kempton et al.[10], in a study of 36 patients, evaluated different treatment strategies for eliminating FVIII inhibitors in patients with mild or moderate hemophilia A. In the analyzed sample, rituximab-based treatments and other immune-modulating approaches showed a higher probability of successful inhibitor elimination than immune tolerance

induction, although without statistical significance. They noted that patients with low inhibitor titers appear to have a higher probability of spontaneous remission without requiring any type of treatment. The conclusions of Van Velzen et al.[3] are along the same lines and support the theory that patients with high-titer inhibitors, such as our patient, appear to benefit more from eradication treatment to prevent future relapses than patients with low-titer inhibitors. It should be noted that patients with certain specific FVIII genotypes, such as R2150H, may have a greater tendency toward inhibitor persistence.[10] In patients with high-titer inhibitors, sustained success was associated with eradication treatment (unadjusted RR, 2.3; 95%CI, 1.3–4.3) compared with no treatment. Nevertheless, the need for an individualized approach to this problem is emphasized,[3] especially now that highly effective therapeutic options are available.[8,9] In our opinion, 2 aspects are key when considering immune-modulating strategies: 1) the increase in patient life expectancy will probably lead to a greater need for surgeries or procedures, with the consequent risk of intensive exposure to FVIII:C and an increased risk of inhibitor development at later ages[2] (Table 2); and 2) immune-modulating or even immunosuppressive strategies entail increased infectious mortality in elderly patients, as can be inferred from studies performed in acquired hemophilia A.[11] In this disease, in which immunosuppressive regimens such as the one received by our patient are used, the main causes of death are hemorrhagic complications and infections. Mortality reaches 9%–33% of cases within the first 2 months, and up to 40% of these deaths are attributable to infections resulting from immunosuppressive treatment.

In our case, given the patient's age and the "alarm" generated in the family, an aggressive immune-modulating strategy and bleeding management with bypassing agents (rFVIIa) were chosen in the presence of a high-titer inhibitor. The option of simple observation associated with bleeding prophylaxis with emicizumab – similar to what is currently advocated in some acquired hemophilia A protocols[12] – was ruled out because we considered that it could take longer to achieve natural tolerance, because there was a risk that tolerance would not be achieved given the high-titer inhibitor, and because of the described risk of relapse. Van Velzen et al.[3], in patients with high-titer inhibitors who received eradication treatment, reported a sustained success rate, with no relapse, of 100%, whereas patients with low-titer inhibitors showed greater variability in response. Some experienced relapses even without eradication treatment; specifically, 35% relapsed after reintroduction of FVIII concentrate following initial disappearance of the inhibitor. In our case, the patient's assessments within the first year after eradication have been negative (< 0.4 BU), although he has not been reexposed to FVIII concentrate beyond the pharmacokinetic study performed to confirm the success of immunosuppression. Regarding the type of product, in patients with mild forms of hemophilia there does not appear to be a relationship between the first product used and the risk of inhibitor development.[13]

Table 2. Main risk factors for inhibitor development in patients with mild hemophilia A

Surgery (OR, 4.2; 95%CI, 1.7–10.3)
FVIII dose > 45 IU/kg (OR, 7.5; 95%CI, 1.36–35.6)
Treatment duration ≥ 10 days (OR, 3.8)

95%CI: 95% confidence interval; OR: odds ratio.
Adapted from Van Velzen et al.[7]

Conclusions

The incidence rate of inhibitor development in non-severe hemophilia A increases progressively with the cumulative number of exposure days to FVIII concentrate, apparently without reaching a plateau,[2,3] unlike what is observed in severe hemophilia A. Inhibitors in this group of patients are a relevant problem, and it is important to establish strategies to reduce risk.[1,4] Knowledge of the causative mutation, maximization of the use of DDAVP or antifibrinolytics, and, when necessary, use of FVIII concentrate doses < 45 IU/kg for the shortest possible time are among the measures cited to reduce the risk of inhibitor development. It is imperative to learn more about the treatment regimens used for eradication and to try to determine the best strategy for achieving immune tolerance.

Immunosuppression appears to be a valid option for the management of high-titer inhibitors,[5] although, with the advent of emicizumab,[8,9,12] the urgency to initiate it is lower, making it possible to defer initiation and choose simple observation, as in the case of low-titer inhibitors. The problem with this second strategy is that, although it makes it possible to confirm inhibitor elimination, confirmation of eradication will also depend on clinical behavior. Further work is needed in the recording and modeling of simple and effective therapeutic

strategies to manage this problem. Finally, individualization is key, as in other areas of care for these patients. Treatment of patients requiring eradication should be decided on a case-by-case basis, because a single approach is unlikely to be appropriate for all.

Funding

None declared.

Conflicts of interest

None declared.

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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REVIEW ARTICLE

Regarding plasma-derived von Willebrand factor concentrates: what about viral safety?

A propósito de los concentrados de factor von Willebrand de origen plasmático: ¿qué decir de la seguridad viral?

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Abstract

We present a brief report on the status of viral safety of plasma derived factor concentrates (pd-FC), especially von Willebrand factor (VWF), in the 21st century. We also present the results of the efforts of the manufacturers and the close observation of guidelines to produce plasma factor concentrates. These efforts and continuous monitoring of these processes allow us to reach a level of safety never achieved before. We remark that this continuous process is necessary to guarantee the safety of a product such as plasma, increasingly necessary in different areas of medicine, focusing on plasma concentrates of VWF (pdVWF). This control is need for products obtained by biotechnology, for which there is less experience.

Keywords: *Biotechnology. Guidelines. Plasma-derived concentrate von Willebrand factor. Recombinant von Willebrand factor. Viral safety.*

Resumen

Presentamos un breve informe sobre el estado de la seguridad viral de los concentrados de factor derivados del plasma, especialmente del factor de von Willebrand, en el siglo XXI. Asimismo, comentamos los resultados en cuanto a cómo los esfuerzos de los fabricantes y la estrecha observación de las directrices para la producción de concentrados plasmáticos de factores, así como la monitorización continua de estos procesos, permiten alcanzar un nivel de seguridad nunca logrado anteriormente. Resaltamos que este es un proceso continuo, necesario para garantizar la seguridad de un producto como el plasma, cada vez más necesario en diferentes áreas de la medicina, centrándonos en los concentrados plasmáticos de factor de Von Willebrand y también en la necesidad de control de los productos obtenidos por biotecnología, con los que existe menos experiencia.

Palabras clave: *Biotecnología. Guías clínicas. Concentrados de factor von Willebrand de origen plasmático. Factor von Willebrand recombinante. Seguridad viral.*

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Date of reception: 04-05-2024
Date of acceptance: 04-06-2024
DOI: 10.24875/RHT.M26000097

Available online: 03-09-2026
Hemost Trombos (Eng). 2026;3(2):61-68
www.revistahemostasiaytrombosis.com

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Introduction

von Willebrand disease (VWD) is the most common hemorrhagic disease in the world, affecting men and women equally,[1] affecting up to 1% of the population according to epidemiological data, although figures based on clinical presentation are close to 0.1%.[2] In milder types of VWD (type 1 and low von Willebrand factor [VWF]), 70–90% of patients are women. In recent years, there have been great advances in terms of improvements in diagnostic techniques, for example, molecular biology techniques or the binding of VWF to collagen or glycoprotein IIb/IIIa. The treatment of bleeding episodes is still basically an on-demand treatment, that is, replacement therapy of the deficient protein (in this case, VWF) for the cessation of bleeding when it occurs. For this purpose, until not so long ago, we used desmopressin (DDAVP) to patient responders, namely Type 1 and some of the Type 2 VWD patients. Other options are VWF of plasma-derived (pd-VWF) origin, with differences in both the content of VWF, the VWF/FVIII ratio, and the structural integrity of the VWF. Itself is reserved to patients not responders to DDAVP or not candidates to DDAVP. The option of recombinant VWF is more recent and has less experience of use. It has important differences in relation to pd concentrates.

Methods

We searched PubMed and Google Scholar with the words viral safety, VWD, and treatment. We have selected those studies with the largest number of patients. We also reviewed the state of the art regarding the infectious risk. This includes measures to minimize it of products obtained from human plasma and those obtained from recombinant technology. Finally, we proceeded to review what has been published by different national and supranational hemovigilance systems and review the concerns about recombinant factor concentrate (FC), especially recombinant VWF.

Discussion

The epidemic derived from the transmission of viral infections by contaminated blood products in the 70 s and 80 s of the last century forced a great effort to improve the process of obtaining the different therapeutic products derived from human plasma on the part of the different companies. This is very important in view of the expected further increase in the volume of plasma required to fractionate and cover clinical needs. This effort has resulted in a very high level of viral safety. On the other hand, extreme vigilance has been exercised to maintain this margin of safety and avoid infectious risks. These risks could be associated with any possible emerging pathogen that enters the plasma reserve in the future. This improvement begins with the appropriate selection of donors, driven by knowledge of viral epidemiology. It continues with the development of blood tests based on molecular diagnosis by polymerase chain reaction techniques. This test, together with viral inactivation techniques in the manufacturing process, is the main measures that contribute to the safety of pathogen transmission.[3,4]

In 2012, Franchini et al.[5] carried out a systematic review, this review included prospective studies published in the preceding 20 years on adverse events (AEs) related to the infusion of FC, of plasma or recombinant origin, on behalf of the European Hemophilia Safety Surveillance System (EUHASS). In his introduction, he points out the high viral safety achieved by FC in the previous 25 years. The greatest safety concern since then had been the development of neutralizing inhibitors to FVIII. In this publication, they consulted electronic databases and article references. AEs related to treatment with plasma and recombinant FC from 1990 to 2011 were collected, excluding inhibitors and thrombotic events on which the main focus had been placed. They reported 946 patients treated with pdFC: 445 Hemophilia A patients, 127 Hemophilia B, and 374 VWD patients. No viral transmissions were reported, which confirms the high degree of safety in this type of concentrate.

In this process of manufacturing pdFC, the inactivation or elimination of viruses[6] occurs during their purification and formulation. Cryoprecipitation, chromatographic separation (particularly immunoaffinity chromatography), and lyophilization remove significant amounts of viruses. Further, it is a key to subject these concentrates to a double viral inactivation process in accordance with EMA standards. These recommend two distinct viral inactivation steps with different modes of action. These steps help to ensure that any virus that survives Step 1 is inactivated and/or eliminated in Step 2. At least 1 of the steps should inactivate or eliminate viruses without a lipid envelope. The guidelines further state that if a manufacturing process contains a step that reliably inactivates and/or removes a wide range of enveloped and non-enveloped viruses, and additional manufacturing steps reliably contribute

Table 1. Purification and viral inactivation methods applied in plasma-derived von Willebrand factor approved in Europe[10]

Product	Manufacturer	Purification	Viral inactivation
Alphanate	Grifols	Heparin ligand chromatography	S/D + dry heat (80°C, 72 h)
Factor 8Y	BioProducts laboratory	Heparin/glycine precipitation	Dry heat (80°C, 72 h)
Fanhdi	Grifols	Heparin ligand chromatography	S/D + dry heat (80°C, 72 h)
Hemate P	CSL Behring	Multiple precipitation	Pasteurization (60°C, 10 h)
Immunate	Baxter	Ion exchange chromatography	S/D + vapor heat (60°C, 10 h)
Wilate	Octapharma	Ion exchange + size exclusion chromatography	S/D + dry heat (100°C, 2 h)
Wilfactin	LFB	Ion exchange + affinity	S/D, 35 nm filtration, dry heat (80°, 72 h)

LFB: Laboratoire Français du Fractionnement et des Biotechnologies; S/D: solvent/detergent.

to the inactivation and/or elimination of the viruses, the second step may not be necessary.[7] A reduction of at least 10 $\log^{10}$ is required for viruses with lipid envelope – a reduction that involves the presence of < 1 viral particle per 1000 L of the plasma pool – and which is considered safe – and of 6 $\log^{10}$ in viruses without this envelope.[8]

A previous publication[9] in 2006 had already highlighted the differences between 12 pd-VWF. The difference is in terms of the number and nature of specific viral safety measures incorporated into the manufacturing processes. Some of these concentrates did not comply with the recommendations of the EMA's Committee for Proprietary Medicinal Products. It was claimed that the viral safety required should be the same for all of them. Tables 1 and 2[10,11] show the different methods used for different pd-VWF approved for use in Europe. Table 3[11], for example, shows the reduction achieved in a widely used pdVWF, such as Wilate® (Lab, Octapharma).[12] This pd-VWF applies two very effective and robust viral inactivation procedures for lipid-enveloped viruses. These procedures are a solvent/detergent treatment (S/D) and prolonged terminal dry heat (called PermaHeat) of the lyophilized product at residual moisture (MR) as recommended. Indeed, it includes one step for non-enveloped viruses, ion exchange chromatography. These steps are aggressive enough to effectively inactivate viruses, above the World Health Organization (WHO)[13] standards (Table 4).[11] The WHO considers that a robust, efficient, and reliable process will be capable of removing or inactivating substantial amounts of viruses, typically four logs or more, being relatively insensitive to changes in process conditions. At the same time, it must be gentle enough to maintain the structural integrity and function of the VWF and FVIII molecules. Emphasis is placed on the need for both physicians and recipients of these concentrates, the patients, to be properly informed about the viral safety of existing products on the market. Finally, potential batch-to-batch contamination is avoided by strict cleaning and disinfection methods as part of the manufacturing process.[14] For this reason, some authors affirm that the experience acquired in recent decades has resulted in the absence of transmission of pathogens by the current generation of blood products.[3] In fact, no case of transmission of viral infection has been reported in the past 30 years or more.

For blood-borne viruses (e.g., human immunodeficiency virus [HIV], hepatitis C virus [HCV], and hepatitis B virus [HBV]), the uninterrupted safety record of solvent-detergent-treated factor (S/D)[15] concentrates makes a strong case to choose it as the method of choice in the manufacture of these products. For pd-VWF, the large molecular size of VWF makes separation by the size of viral particles (by nanofiltration, for example) less feasible. In this case, one step in the manufacturing process should be effective for hepatitis A virus (HAV) at least. Heat inactivation procedures, such as pasteurization or Permaheat, have proven to be effective against HAV. These methods are effective even for other more resistant viruses such as parvovirus B19.[6] There are no transmissions of human transmissible spongiform encephalopathies (TSE) agents by plasma derivatives. The problem is that analytical methods capable of detecting the prion in affected human brains or in other tissues are not capable of detecting the agent in blood or plasma.[15] This suggests that, if present, the amount found would be very low and the

Table 2. Virus inactivation and/or removal methods for plasma-derived vWF concentrates[11]

Brand name (manufacturer)	Precipitation	Chromatography*	Pasteurization	S/D	Dry heat	Lyophilization
Alphanate/Fanhdi (Grifols)	x	x*	x	x	x	x
Biostate (CSL)	x	x†	x	x	x	x
Humate-P/Hemate-P (CSL Behring)	x		x			x
Koate DVI (Talecris Biotherapeutics)	x			x		x
Wilate octapharma	x‡			x	x	x

*Immunoaffinity chromatography.
†Size-exclusion chromatography.
‡Ion-exchange chromatography.
vWF: von Willebrand factor; S/D: solvent/detergent.

Table 3. Pathogen inactivation/elimination by Wilate® manufacturing process[11]

Pathogen	HIV	HBV	HCV	WNV	HAV	B19	vCJD
Model used	HIV-1	PRV	SBV	SBV	HAV	PPV	HAS 263 K
Step	Logarithmic reduction factor [log_{10}]						
Sequential precipitations							1.8
Ion exchange chromatography					1.9	3.3	
Sequential chromatography purifications							2.4
S/D treatment	≥ 7.5	≥ 8.5	≥ 8.6	≥ 8.6			
PermaHeat treatment*	≥ 5.8	4.9	≥ 5.5	≥ 5.5	≥ 5.7	4.1	
Total	≥ 13.3	≥ 13.4	≥ 14.1	≥ 14.1	≥ 7.6	7.4	4.2

*100°C 2 h.
HIV: human immunodeficiency virus; HBV: hepatitis B virus; HCV: hepatitis C virus; WNV: West Nile virus; HAV: hepatitis A virus; B19: human parvovirus B19; vCJD: variant Creutzfeldt–Jakob disease; PRV: pseudorabies virus; SBV: sindbis virus; PPV: porcine parvovirus; HAS: hamster adapted scrapie; S/D: solvent/detergent.

capacity of plasma fractionation. The purification processes applied to coagulation products to eliminate TSE agents are based on the physicochemical change of properties caused by the conversion of the natural form of prion protein (PrPc; rich in a-helix) to pathological form (PrPTSE; rich in b-sheets).[16] This implicates new different properties such as insolubility or hydrophobicity providing the basis for its elimination during manufacturing steps. Besides, the production of plasma products includes many steps with a capacity to eliminate impurities and other different pathogens.

Heat treatment is a widely used method.[7] Viruses have a variable sensitivity to heat. The efficacy of heat in viral inactivation depends on variables such as time, physical state (dry or in solution), saline content, the reason for the temperature change, or the nature and concentration of the stabilizers. The temperature is important; if < 80°C is relatively ineffective against some viruses in lyophilized products. Heat can be applied to freeze-dried concentrates at higher temperatures (80-100°C), from half an hour to 72 h. Other stages, such as pasteurization, apply heat treatment to the product in aqueous solution at 60° for 10 h. Both types of stages have been shown to be effective against enveloped and non-enveloped viruses,[14] as can be seen in table 4. Here showed the logarithmic reductions for each virus model of different stages of viral inactivation and purification.

As previously discussed, the EMA[7] requires pd-FC to have several stages of viral inactivation/reduction. These must be aggressive enough to guarantee the viral safety of the product. At the same time, they must be respectful of the structural integrity of the proteins of interest.[8] To meet these two premises, each manufacturer designs or chooses these stages of viral inactivation and purification to achieve the greatest safety and

Table 4. Virus reduction factors (log) for relevant viruses reported for individual process steps[11]

Process step evaluated	Virus reduction factors (log)									
	Enveloped viruses				Non-enveloped viruses					
	HIV	HCV model	HBV model		HAV and model		B19V and model			
	HIV-1	BVDV	BHV	PRV	HAV	POL	B19V	PPV	CPV	MMV
Lyophilization	1.2	1.7	1.3	-	2.1	3.4	-	< 1.0	-	-
Cryoprecipitation	-	-	-	1.6	1.5	-	-	1.5	-	-
3.5% PEG precipitation	< 1.0	< 1.0	< 1.0	-	-	3.3	-	1.2	-	-
Al (OH) 3 adsorption/glycine precipitation/NaCl precipitation	3.6	2.4	-	3.7	2.4	-	-	3.4	-	-
S/D	≥ 11.1	≥ 4.5	≥ 8.0	≥ 8.5	NA	NA	NA	NA	NA	NA
Dry heat	5.2†	≥ 4.9†	2.1†	4.9§	≥ 5.8*	≥ 2.5*	4.1‡	4.1†	-	-
Pasteurization§	≥ 6.4	≥ 8.9	-	4.6	4.2	-	≥ 3.9	1.1	-	-
Chromatography	≥ 2.0	< 1.0	7.6	-	-	< 1.0	-	< 1.0	-	-
Virus filtration	> 6.4¶	6.6**	-	> 6.0¶	6.8**	-	-	-	≤ 1.0¶	-
Vapor heat	> 6.8	> 7.1	-	> 7.4	> 4.5	-	≥ 3.5††	-	≤ 1.0	-

Hyphens indicate that no data are available.
*100°C for 30 min.
†80°C for 72 h.
‡100°C for 120 min.
§In aqueous solution at 60°C for 10 h.
¶35-nm filtration.
**35- to 15-nm sequential filtration applicable.
††60°C for 500 min, followed by 80°C for 60 min.
BHV: bovine herpes virus (a nonspecific model virus for HBV); CPV: canine parvovirus (a model virus for B19V); MMV: mice minute virus (a model virus for B19V); NA: not applicable; PEG: polyethylene glycol; POL: poliovirus Sabin type 2; human parvovirus B19.

efficacy of its products, depending on the pathology for which they were designed, as can be seen in table 3.[11]

In relation to the viral transmission associated with the use of pd-VWF, no cases are reported in this publication by Kouides et al.[17] in the period from 1982 to 2015. A total of 670 AEs were reported. 343 AEs corresponded to adverse reactions considered clinically relevant risks adverse drug reactions (ADRs) and 103 suspected virus transmission. None of the suspected cases was confirmed as associated with the infusion of the pd-VWF in question. The analyzed concentrate was subjected to viral inactivation by pasteurization at 60°C for 10 h in the presence of stabilizers before a second precipitation with sodium chloride.[18] Escuriola-Ettingshausen et al.[19] in a systematic review of the literature evaluated the existing evidence on, among others, the safety of a pd-VWF in the treatment of VWD. They incorporated an analysis of pharmacovigilance data collected over more than 40 years. They identified a total of 1296 ADRs in the database from June 1982 to June 2022, but any confirmed cases of viral transmission.

A retrospective study by Jiménez-Yuste et al.[20] in 2022 also evaluated the safety, among other items, of a pd-VWF in the management of VWD in Spain. This product is subjected to two viral inactivation steps: S/D (using a combination of TNBP and polysorbate 80) and terminal heat at 80°C for 72 h after lyophilization. The time period runs from July 2019 to February 2020. 15 AEs were reported in eight of 72 patients. None was related to possible transfusion transmission of viral infections.

Federici et al.,[21] reported the results of a retrospective analysis of the efficacy and safety of a pd-VWF in 10 centers in Italy. The data were collected from the medical records of 57 patients. The time period runs from January 2017 to December 2019. They did not reported significant AEs, including the transmission of viral infections. Rugeri et al.[22] conducted a systematic review on efficacy and safety of the same product for the treatment of VWD patients. They selected 11 publications from eight study cohorts, all from multicenter trials with pediatric and adult patients. They included pharmacovigilance data reported from clinical trials and on

246 patients receiving the pd-VWF. The authors reported 34 AEs in 24 patients, but no cases of viral transmission related to use of these concentrates. In addition, pharmacovigilance data from 23 years were included in relation to 5877 patients, reporting 150 cases. These cases corresponded to 378 ADRs, but the transmission of any viral infection with the use of this pd-VWF was also not reported.

In 2020, the results of a prospective, observational, post-marketing study of another pd-VWF in relation to the treatment of VWD were reported. They evaluated, among other items, the safety in 158 of the included patients. These patients belonged to 31 centers in France. AEs were reported in 21.5% of patients. None were considered related to the treatment itself. No safety alerts were reported from an infectious point of view.[23]

In 2021, it was reported the results of WIL-20 study. This is a prospective, observational, phase 4, and post-marketing study. It was designed to evaluate safety, tolerability, and efficacy of a pd-VWF in routine clinical practice. It included patients of all ages with all types of VWD in various settings.[24] Over a 2-year period (2015-2017), out of 120 included patients, only 111 were selected for safety evaluation. No cases of transmission of viral infections were reported in 7024 infusions of this product. In addition, in the latest Food and Drug Administration (FDA) report[25] evaluating the safety of this pd-VWF from September 2019 to April 2022, no seroconversion was reported in the USA.

The latest data reported from EUHASS[26] to 2022 include 4641 AEs since 2008. No cases of viral infection transmitted by the use of pd-FC were reported, included pd-VWF. This safety is reinforced, for example, by the dates reported from different registries: in the United Kingdom alone, between 2022 and 2023, 68,892,532 international units of VWF were transfused, in 1034 patients. No incidence was reported from an infectious point of view.[27]

These data effectively contrast with the infectious risks of other blood products used daily in our hospitals, such as apheresis platelets or red blood cell concentrates. These are not subjected to viral inactivation processes used in pd-FC. An US publication retrospectively analyzed the transmission of viral infections by transfusion of contaminated blood products in the hospital. The time period runs between 2013 and 2018. It reported an infection rate of 1/225,440 units transfused.[28] Spanish hemovigilance system reports no viral infections associated with transfusion of blood components in 2021. In 2020, transmission was confirmed in one case of West Nile virus (WNV), without clinical consequences, or in 2019, one case of cytomegalovirus and one case of HEV.[29]

Cases of positive antibodies to some viruses are reported[17,22,24,25] as is the case in the general population, especially those that are easier to transmit such as parvovirus B19. The batches involved were certified to be virus free after comparing and analyzing. It is ruled out that these few reported viral infections can be attributed to treatment with the product in question. The lower requirements demanded by the WHO[13] or EMA[7] for viruses such as HAV or parvovirus B19 are based in two facts: first, on their lower risk to humans as they do not generally lead to chronicity of symptoms and second, on the potential presence of neutralizing antibodies in the plasma pool of untranslated infection.[8]

Conclusion

With all that said, from the point of view of viral safety, it can be said that pd-FC, including pd-VWF, is safer than ever before.[3] At the present time, the possibility of infection by HBV, HCV, and HIV, combined with general and universal case vaccination against HAV and HBV, especially in first-world countries, is rather theoretical.[30] Thanks to these improved and comprehensive steps for the reduction of pathogens, doctors and patients should be confident in the efficacy and safety of these FC[14] for, among others, the treatment of VWD. As a result of the work carried out, no case of transmission of any viral infection by transfusion of pd-FC has been reported over the past 30–40 years. Further, and unlike what has happened in hemophilia, efforts to obtain a recombinant VWF (rVWF) have been less successful. At present, only one approved rVWF has been obtained.[31] In the past 35 years, the transmission of viral infections with the use of products obtained by recombinant technology not reported. It is known that these concentrates could theoretically transmit human or non-human mammalian viruses. These viruses would be introduced through the stem cell lines or by human or animal proteins contained in the liquid medium used for freezing or culturing the cells.[5,6] This risk is considered real,[6] more so for products obtained from human cell lines than those from animal cell lines (such as, Chinese hamster ovary [CHO] cells). They must be subjected to the same viral inactivation processes as pd-FC. Barone et al.[4] underline the importance of the choice of cell line once the reported contaminations have been detected. Four of five viruses identified in human and primate cell lines are human and primate pathogens. Only one (the Cache Valley virus) that caused contamination of CHO cell

cultures is known to cause infection in humans.[5] Manufacturers are aware of these differences in risk associated with the cell line used. Testing is critical to determining viral safety in biotech products but this alone does not guarantee safety. It is important to adopt an holistic and multifaceted approach. This fact was highlighted by severe acute respiratory syndrome coronavirus 2 pandemic, whose ability to infect production cell lines or to be detected with existing assays was not initially known. Therefore, the viral safety of some biotechnological products, today, depends almost exclusively on the prevention of contamination through rigorous controls of the manufacturing process. As previously stated, recombinant FC must be subjected to the same viral inactivation processes as products of plasma origin.[4,5,7] Transmission of viral infections with rVWF has not been reported so far.

The appearance of the first rVWF is one more therapeutic element to add to the current arsenal. Its appearance does not respond in any way to a question of viral safety. It leaves open questions such as superiority in terms of clinical efficacy or potential immunogenic risk. Other questions are related to cost and how it can impact the sustainability of health systems, at least, those financed with public resources. Given the clinical efficacy of current pd-VWF, and with the accumulated experience of use, other issues, especially inhibitor development in hemophilic patients, are a much more real concern, not viral safety. The effort continues to prevent the entry of any emerging pathogens into the much-needed plasma reserves. In our opinion, until we find a test, and only depending on the plasma source not languishing, we can and should ensure that our patients are being treated with safe and effective pd-FC as they have done so far. We cannot forget that not even the recombinant FC, even though it avoids the use of proteins in its composition, excludes 100% of the possibility of contamination of cell lines. However, no cases of viral transmission have been reported with these recombinant concentrates. Therefore, the no possibility of transmitting infections of viral or other origin to humans should not be the only valid argument to justify its use. It should demonstrate efficacy and efficiency at least similar to that of the products currently used to treat VWD. Admittedly, this can be complicated and beyond the scope of this report. Leebeek et al.[31] recognize that rVWF prophylaxis maintained a similar level of hemostatic control in patients switching from pdVWF prophylaxis to rVWF prophylaxis, not better. In fact, on pd-VWF prophylaxis, 37.5% of patients had more than two BEs and 25% had no BEs. After switch to rVWF, 62.5% had more than two BEs and 37.5% had no BEs. As said Dr Klamroth[11], 10 years ago, and especially when it is not clear that these new recombinant products bring any real net benefit, certainly not in terms of effectiveness and probably, efficiency, all of us should rely not only on the proven efficacy but also on the safety of this pd-VWF for treatment of VWD. Although some cases of positivity have been described, for example, to parvovirus B19, it has been highlighted that the current requirements for this virus by regulatory agencies are adequate. No alarm situation should be generated for our patients. Therefore, zero risk is never guaranteed, but even so, pd-FC never had a wider safety margin than today, comparable to any existing biologically derived therapeutic product, in terms of theoretical risks of biological agent transmission. This is amply covered by millions and millions of units transfused to patients in the past 25–30 years. Any incidence has been reported as derived from the reports of EUHASS, British surveillance systems or the FDA itself, regardless of the manufacturer and/or product. In our opinion, in the light of the data, we believe that viral safety, at least as far as known pathogens are concerned, is fully guaranteed. This cannot be an excuse to reduce the efforts made by the industry, in all phases of the process of obtaining plasma derivatives. They are carried out to ensure both the safety and efficacy of the final product.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The authors declare to have followed the ethical standards of the relevant experimentation committee, according to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

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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REVIEW ARTICLE

Reflections on the importance of factor VIII and von Willebrand factor pharmacokinetics in the safety and efficacy of current von Willebrand factor concentrates

Reflexiones sobre la importancia de la farmacocinética de los factores VIII y von Willebrand en la seguridad y la eficacia de los actuales concentrados de factor von Willebrand

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Abstract

Prophylaxis in von Willebrand disease is addressed, focusing on the composition and efficacy of von Willebrand factor concentrates.Three products with different characteristics in terms of their origin and composition (Veyvondi®, Wilate®, and Wilfact®) are compared, highlighting their differences in weekly consumption, infusions and thrombotic events. The results indicate that Wilate® has a lower weekly intake and comparable efficacy in reducing bleeding. The accumulation of factor VIII and its relationship with thrombotic risk are discussed, underlining the importance of precise dosing to maximize efficacy and minimize safety and economic risks.

Keywords: *von Willebrand disease. Prophylaxis. FVIII/VWF ratio. Randomized controlled trials. Thrombin generation.*

Resumen

Se aborda la profilaxis en la enfermedad de von Willebrand, enfocándose en la composición y la eficacia de los concentrados de factor von Willebrand. Se comparan tres productos con características diferentes en cuanto a su origen y composición (Veyvondi®, Wilate® y Wilfact®), destacando sus diferencias en consumo semanal, infusiones y eventos trombóticos. Los resultados indican que Wilate® tiene un menor consumo semanal y una eficacia comparable en la reducción de sangrados. Se discute la acumulación de factor VIII y su relación con el riesgo trombótico, subrayando la importancia de la dosificación precisa para maximizar la eficacia y minimizar riesgos de seguridad y económicos.

Palabras clave: *Enfermedad de von Willebrand. Profilaxis. Ratio FVIII/FVW. Ensayos clínicos controlados. Generación de trombina.*

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Date of reception: 09-07-2024
Date of acceptance: 16-07-2024
DOI: 10.24875/RHT.M24000011

Available online: 03-09-2026
Hemost Trombos (Eng). 2026;3(2):69-73
www.revistahemostasiaytrombosis.com

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Introduction

Long-term prophylaxis in the context of von Willebrand disease (VWD) is an area of growing interest regarding its management, especially in patients with a severe or frequent bleeding phenotype. Despite the scarcity of prospective, controlled studies evaluating the efficacy of this therapeutic option, there is significant discrepancy surrounding the composition of von Willebrand factor (VWF) concentrates. These VWF concentrates may or may not contain factor VIII (FVIII), and among the VWF concentrates with FVIII, differences have been reported in the FVIII: VWF ratio. Finally, it is also unclear what the most appropriate FVIII: VWF ratio is in terms of treatment efficacy.

VWF concentrates were originally developed for the treatment of hemophilia A and are used in patients who do not respond to desmopressin or when it is contraindicated. The available concentrates can be of plasma-derived or recombinant origin. The only recombinant VWF concentrate (rVWF), Veyvondi®,[1] only contains VWF and is obtained from a Chinese hamster ovary cell line. Plasma-derived VWF concentrates can be categorized by their varying purity. Wilate®[2] is a high-purity concentrate, with FVIII in a FVIII: VWF ratio of 1:1, while Wilfact®[3] is a pure VWF plasma concentrate (FVIII: VWF < 0.2:1). Due to differences in the manufacturing process, design, and factor ratio[4] (Table 1), it is important to know their precise dosing, given the implications this can have on the safety and efficacy of these concentrates, as well as on the financial impact it may have on the hospital pharmacy.

Method

Based on published scientific evidence, we compared the median annual bleeding episodes (annualized bleeding rate [ABR]), the median weekly consumption (in IU of ristocetin cofactor activity [VWF: RCo]/kg), and the median weekly infusions for long-term prophylactic treatment with the 3 above-mentioned VWF concentrates, as well as their safety surrounding thrombotic events. These 3 concentrates were chosen once data from prospective studies evaluating, among other things, the efficacy of prophylaxis were used for comparison purposes. For Veyvondi®, post-hoc analysis data from the prospective clinical trial NCT02973087 were considered[1], and for Wilate®, data from the prospective clinical trial NCT04052698 were taken into consideration[2]. For Wilfact®, data were taken from a prospective post-marketing observational trial.[3] Efficiency analysis of the 3 VWF concentrates was also conducted using generative artificial intelligence (ChatGPT-4®).

Results

When evaluating the results, Wilate® shows lower weekly consumption vs pure VWF concentrates, Veyvondi® and Wilfact® (median of 58, 92.6, and 87 IU/kg, respectively). The median weekly infusions for the 3 products are the same (2), without loss of efficacy (ABR 1.9, 2.35, and 1, respectively). Regarding thrombotic events, none have been reported with Wilate® throughout its clinical development in more than 200 patients,[2,5-7] nor with Wilfact®. One case of deep vein thrombosis was reported in 1 leg during major hip replacement surgery with Veyvondi® (Table 2).[8]

To determine the efficiency of the 3 products, ChatGPT-4® considered the reduction in the bleeding rate and the median reported consumption of VWF after analyzing the 3 reports. According to ChatGPT-4®, Wilate® could be considered the most efficient due to its lower weekly consumption and efficacy in reducing bleeding, although Veyvondi® also shows excellent efficacy in terms of bleeding reduction.

Discussion

One of the greatest challenges in managing VWD, aside from hemostatic management, is the accumulation and monitoring of FVIII, especially in cases of intensive treatment, such as after a severe trauma or surgery. FVIII levels > 150% are thought to be associated with a higher thrombotic risk.[9]

It would seem logical somehow to think that the use of pure VWF concentrates would be free from this risk. However, thrombotic events have been reported during scheduled surgical procedures in the clinical development of Veyvondi®,[5] as well as with other VWF/FVIII concentrates with a lower FVIII proportion than Wilate® (e.g., Haemate-P® with a VWF: FVIII ratio of 2.4:1, Fanhdi/Alphanate®).[10,11] Thrombotic risk due to FVIII accumulation does not seem to be due to the presence or absence of FVIII in the VWF concentrate, but rather could be due to the different pharmacokinetic behavior of the 2 factors in these products. Free VWF (pure VWF concentrates or those with a lower proportion of FVIII than VWF) causes a delayed elevation of FVIII levels, peaking at 12–24 hours (Fig. 1).[12] In the case of intensive treatment, such as in surgery, especially major surgeries, this phenomenon could cause FVIII

Table 1. Content of VIII, VWF, and the VWF/FVIII ratio in various FVIII concentrates

Product	FVIII (IU/mL)	VWF (IU/mL)	VWF/FVIII
Intermediate purity			
Haemate-P®	28	71	2.5
Profilate SD®	45	145	3.2
Kryobulin TIM3®	33	157	4.8
High purity			
Octavi®	23	14	0.6
Koate HP®	156	144	0.9
Immunate®	85	74	0.9
Beriate®	25	4.3	0.2

FVIII: factor VIII; VWF: von Willebrand factor.
Adapted from Berntorp.[4]

Table 2. Consumption, efficacy, and infusion frequency of analyzed VWF concentrates

Parameters	Veyvondi®[1]	Wilate®[2]	Wilfact®[3]
Consumption (IU VWF/kg), median	92.6	58	87
Weekly frequency, median	2	2	2
ABR, median	2.35	1.9	1

VWF: von Willebrand factor; ABR: annualized bleeding rate.

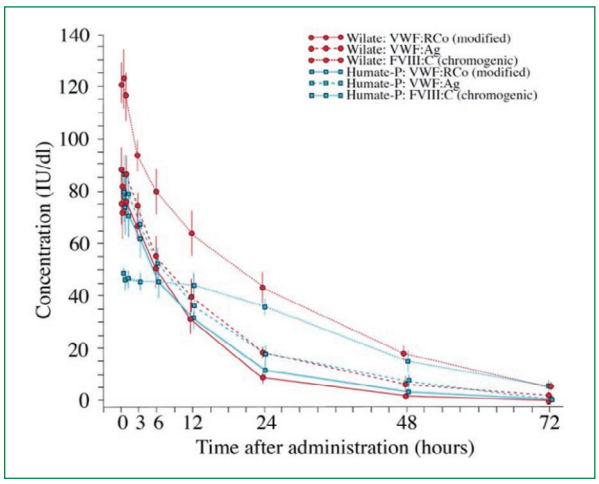


Figure 1. Mean plasma concentrations for VWF and FVIII in subjects with type 3 VWD after the administration of Wilate® and a VWF-rich VWF concentrate (*adapted from Kessler et al.*).[5] The observed decay curves for VWF: RCo are similar between Wilate® and HumateP® for subjects with type 3 VWD; the FVIII: C curves are markedly different. For Wilate®, a nearly parallel decrease throughout time is observed for VWF: RCo and FVIII. For Humate-P®, after peaking, the FVIII curve shows a plateau of approximately 12 hours. VWF: von Willebrand factor; FVIII: factor VIII; VWD: von Willebrand disease; RCo: ristocetin cofactor activity; C: coagulant activity.

accumulation. With Wilate®[13] (VWF/FVIII ratio 1:1), all VWF is completely saturated with FVIII, so it cannot bind to the patient's endogenous FVIII. Immediately after infusion, the FVIII peak coincides with the VWF peak, and both factors are eliminated at the same rate,[5,13] without sustained FVIII accumulation in intensive treatment situations.[5]

In terms of bleeding prophylaxis efficacy, the 3 VWF concentrates achieve acceptable ABRs. Although the median number of weekly infusions is the same for all of them (2), weekly consumption in IU of VWF: RCo differs significantly, being lower for Wilate®.[1-3] Why? Firstly, it could be due to the presence of FVIII leading to higher thrombin peaks. In fact, Rugeri et al.[12] reported that a low thrombin peak was associated with a higher risk of bleeding in patients with VWD, and their results suggest that the delay and reduction in thrombin generation in VWD could probably be mainly attributed to a decrease in FVIII plasma concentration in patients with this disorder (Figs. 2 and 3). Berger et al.[13] reported a reduction in total ABR (from 7.5 down to 2) after switching to Wilate® in a type 3 VWD patient previously on Wilfact® prophylaxis 3 times/week (42 IU/kg dose), maintaining a similar prophylaxis regimen.

Secondly, the difference in thrombin peaks generated with Veyvondi® and Wilate® could be due, sames as FVIII accumulation, to the interaction and pharmacokinetics of VWF and FVIII. In the case of rVWF, while the infused exogenous VWF is eliminated (half-life of, approximately, 12–15 hours), endogenous FVIII takes longer to normalize and does not peak until 12–24 hours (Fig. 3),[7,13] when the amount of VWF is lower. With Wilate®, the obtained FVIII peak is higher and reached right after infusion, coinciding with the VWF peak and favoring the formation of a higher thrombin peak.[13]

In fact, this likely impacts the efficacy of the products; Leebeek himself[1] states that "rVWF prophylaxis maintained a similar level of hemostatic control in patients who switched from plasma-derived VWF prophylaxis to rVWF prophylaxis," not superior.

Finally, in terms of efficiency, the unit cost of the products (Veyvondi® is pending reimbursement price in Spain) nor the fact that in some situations, Veyvondi® may require co-administration of FVIII concentrates within the first 24 hours,[2] – an aspect that should

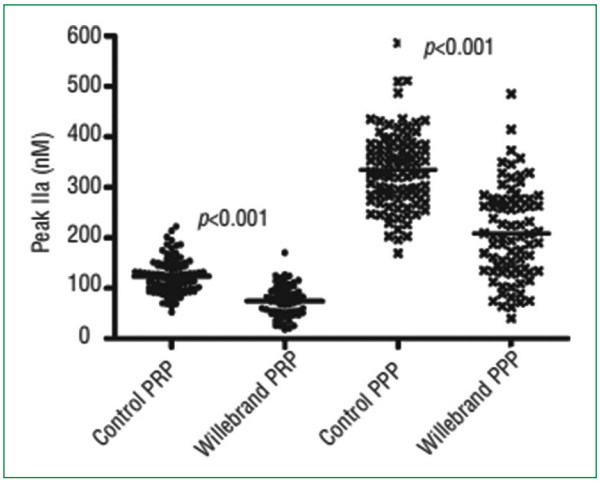


Figure 2. Maximum thrombin generation values in patients with VWD and controls *(adapted from Rugeri et al.).*[12] Peak IIa (thrombin peak): thrombin peak; PPP: platelet-poor plasma; PRP: platelet-rich plasma.

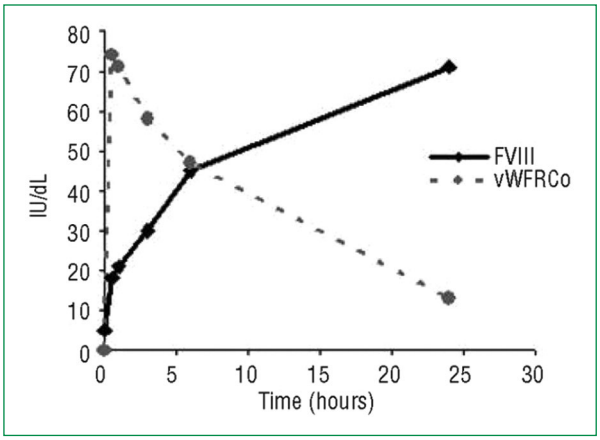


Figure 3. Progression of VWF and FVIII levels after the administration of FVIII-poor VWF concentrates (*adapted from Rugeri et al.*).[12] VWF: RCo: von Willebrand factor ristocetin cofactor activity; VWF: von Willebrand factor; FVIII: factor VIII.

obviously negatively impact the product efficiency – has not been considered in the analysis.

Conclusions

Recognizing the limitations this approach may present, this analysis seems to support the idea that the balance between FVIII and VWF in the content of VWF concentrates may be key in terms of safety, efficacy, and efficiency, the long-term treatment and prophylaxis of VWD, and in the financial implications associated with treatment. However, more controlled clinical trials with sufficiently large numbers of patients are needed to confirm these observations and help clinicians select the most appropriate VWF concentrate for bleeding treatment and prophylaxis in patients.

Funding

None declared.

Conflicts of interest

None declared.

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 they have indeed used generative artificial intelligence, specifically ChatGPT-4, for the efficiency analysis of the 3 treatments, through the analysis of the results reported in the different studies.

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SCIENTIFIC LETTER

Emicizumab in acquired hemophilia A: a case report

Emicizumab en hemofilia adquirida A: a propósito de un caso

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Acquired hemophilia A (AHA) is a rare autoimmune coagulopathy, with an estimated incidence rate of 1 to 6 cases per million inhabitants per year, although this is probably underestimated because of the lack of diagnostic suspicion and the concomitant use of anticoagulants or antiplatelet agents in the affected population.[1] It predominantly affects elderly individuals, with a median age at diagnosis of 65 years and a biphasic distribution: a first peak in young women during the puerperium, and a second peak in individuals > 60 years, with no sex differences.[1] It is characterized by the development of neutralizing autoantibodies against coagulation factor VIII (FVIII), leading to spontaneous bleeding, which is often severe.

In more than 50% of cases, AHA is idiopathic. Identified underlying causes include systemic autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and Sjögren syndrome; solid tumors, including lung, prostate, colon, and pancreatic cancer; hematologic malignancies, such as non-Hodgkin lymphoma, chronic lymphocytic leukemia, and multiple myeloma; the postpartum period; and certain drugs, including penicillins, interferons, and fludarabine. Occasionally, cases related to infections, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have been described.[1,2] Mortality associated with AHA ranges from 7 to 38% depending on the series, with most fatal events occurring within the first two months after diagnosis: uncontrolled bleeding predominates in the early phases, whereas infections due to immunosuppressive (IS) treatment are the leading cause of late death.[1,3]

The management of AHA is complex and challenging for several reasons. First, diagnosis is often delayed because bleeding is confused with bleeding secondary to anticoagulant or antiplatelet therapy. Second, bleeding risk does not correlate with inhibitor titer or residual FVIII levels, which makes individual risk stratification difficult. Third, the IS treatment required to eradicate the inhibitor, usually corticosteroids alone or in combination with cyclophosphamide or rituximab, entails relevant toxicity in an already frail population, with a high prevalence of comorbidities, opportunistic infections in up to 30% of cases, and infection-attributable mortality ranging from 15% to 47% in different registries.[1,3,4]

Classically, hemostatic treatment is based on 2 categories of agents. Bypassing agents, recombinant activated factor VIIa (rFVIIa, NovoSeven®) and activated prothrombin complex concentrate (aPCC, FEIBA®), are the first-line standard, with efficacy of approximately 60–90%.[1,2] In the Spanish registry,[3] 70% of patients required hemostatic treatment, with rFVIIa being the most frequently used product (60.3% of cases), at a mean dose of 90 μg/kg per episode, a median of 15 doses, and a median duration of 7 days. Second, in patients with a low inhibitor titer (< 5 BU/mL), the use of high-dose human FVIII concentrates, up to 100–200 IU/kg, may be considered with the aim of

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Date of reception: 04-09-2025
Date of acceptance: 07-05-2026
DOI: 10.24875/RHT.M26000092

Available online: 03-09-2026
Hemost Trombos (Eng). 2026;3(2):74-78
www.revistahemostasiaytrombosis.com

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overcoming inhibition, although their efficacy is limited and the required doses are considerably high.[1,2] In the EACH2 data series, the efficacy profile of FVIII concentrates was 34%, compared with 93% for bypassing agents.[2] Recombinant porcine factor VIII (susoctocog alfa, Obizur®) represents a valuable alternative, with 86% efficacy in the pivotal study, and is particularly useful when the inhibitor does not show significant cross-reactivity with the porcine antigen.[1] Finally, tranexamic acid may be used as an adjunct, especially in mucocutaneous bleeding or as the sole agent in minor bleeding, although its combination with aPCC increases thrombotic risk and should be assessed individually.[1,5]

IS treatment for inhibitor eradication includes different drugs, either alone or in combination: corticosteroids, cyclophosphamide, and rituximab, an anti-CD20 antibody. In the Spanish registry,[3] IS was administered in 96.6% of patients, with the combination of steroids and cyclophosphamide being the most widely used regimen (45.4%), and with a median time to complete remission of 49 days (IQR, 34–89 days). The main causes of death in these patients are usually infections, 9.9% in the Spanish registry, and uncontrolled bleeding, 3.3%, generally associated with very high inhibitor levels and low FVIII activity. In fact, an inhibitor titer ≥ 20 BU and FVIII activity < 1% are considered poor prognostic factors at diagnosis.[2,3,4]

In recent years, evidence has emerged supporting the use of emicizumab in this condition, given the results shown in the management of congenital hemophilia with inhibitors.[5] Emicizumab is a bispecific monoclonal antibody that replaces the function of FVIII in the tenase complex, restoring thrombin generation.[6] Several reports have shown its efficacy in bleeding prophylaxis in patients with acquired hemophilia, reducing the need for bypassing agents.[7-10] In some cases, it has been suggested that the use of emicizumab could reduce the need for IS by allowing time for natural immune tolerance to be achieved.[7] Our objective is to report the experience with emicizumab in this context in a patient from our center. To this end, data were collected from the patient's electronic health record.

Case report presentation

A 90-year-old man was admitted for scheduled laparoscopic left colectomy in the setting of moderately differentiated colorectal adenocarcinoma (G2). The patient was receiving antiplatelet therapy with acetylsalicylic acid 100 mg/day because of a transient ischemic attack in 2021, and this was not discontinued before surgery. In the immediate postoperative period, the patient presented with rectal bleeding and progressive anemia requiring multiple transfusions. The coagulation study showed prolonged activated partial thromboplastin time (aPTT), which corrected in the immediate mixing study, accompanied by decreased coagulation factors, except factor IX. Transfusion of fresh frozen plasma (FFP) was initiated at 10–15 mL/kg/day, without resolution of bleeding.

Of note, the FVIII inhibitors characteristic of AHA are time- and temperature-dependent in their inhibitory action; therefore, aPTT and mixing studies require prolonged incubation, 2 hours at 37 °C, to demonstrate their inhibitory effect.[1] In the case presented, the aPTT probably corrected in the initial mixing study because this prior incubation had not been performed, which delayed the diagnosis. Only after reviewing the past medical history and noting that the aPTT had been prolonged for approximately 6 months was the mixing study repeated with 2-hour incubation, showing a low-titer inhibitor against FVIII (4 BU).

Several reassessment colonoscopies showed only mild, diffuse bleeding in the anastomotic area, managed with clips and local hemostatic agents; however, rectal bleeding persisted. In this context, an oncologic patient with recurrent bleeding and previously prolonged aPTT, the possible presence of a coagulation inhibitor was suspected. Lupus anticoagulant was negative, and the remaining intrinsic pathway factors and von Willebrand factor were within the normal range. A diagnosis of probably secondary AHA was established in the context of the oncologic process. Chromogenic FVIII was higher than coagulant FVIII (29 vs. 69%), a characteristic finding of IgG4-type inhibitors in AHA.

To control active bleeding, in addition to discontinuing antiplatelet therapy, rFVIIa, recombinant activated factor VIIa, was indicated at 90 μg/kg every 2–3 hours, with progressive spacing until discontinuation after 5 days. The alternative use of high-dose human FVIII concentrate was not considered first choice because rFVIIa was available and, given that the inhibitor was time-dependent, the FVIII doses required to overcome inhibition would have been extremely high, 100–200 IU/kg or more, with little guarantee of efficacy.[1] Recombinant porcine factor VIII, susoctocog alfa, was not used in this case because it was not available at the center at that time. In parallel, IS was initiated with prednisone 1 mg/kg/day for 7 days, and compassionate use of

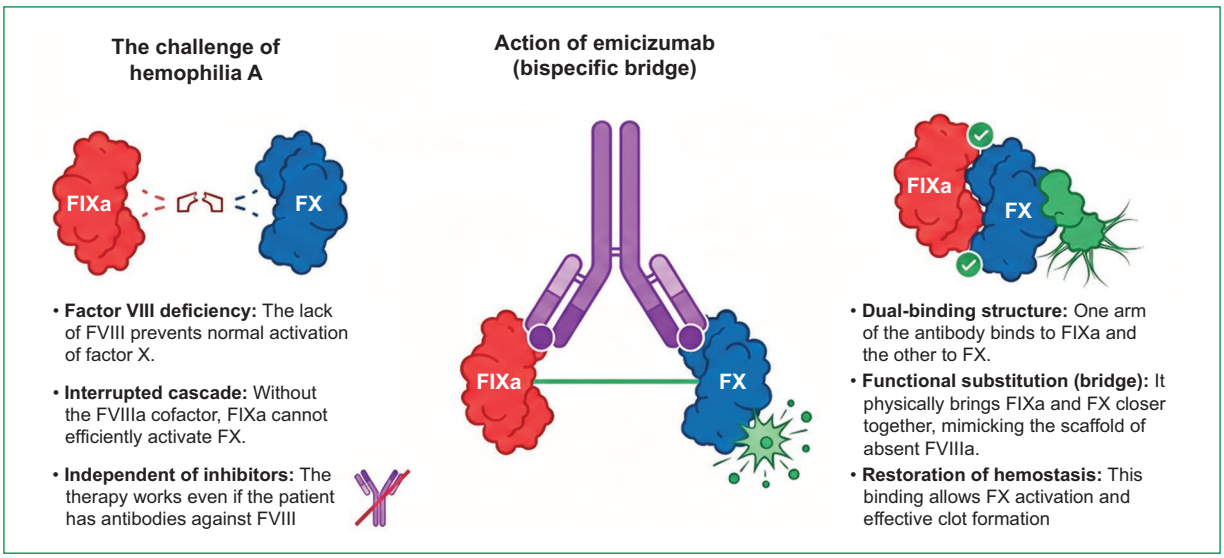


Figure 1. Mechanism of action of emicizumab (*image generated with NotebookLM*). FVIII: factor VIII; FX: factor X; FIXa: factor IV activated.

emicizumab, off-label, was requested for prophylaxis of inhibitor-associated bleeding (Fig. 1).

The regimen used was that described in the prospective AGEHA study, which allowed authorization of the drug in Japan for this indication[10]: dose 1 (D1), 6 mg/kg subcutaneously; dose 2 (D2), 3 mg/kg at 24 hours; and subsequently weekly maintenance at 1.5 mg/kg. Of note, there is no globally approved standard emicizumab dosing regimen for patients with AHA, and the regimen used in this case was derived from the above-mentioned prospective study and from the recommendations of the GTH working group.[7,10] The high cost of emicizumab should also be mentioned, as it may limit its use in routine clinical practice, particularly in patients without clinically relevant bleeding and in whom the benefit-cost ratio is not clearly favorable.

When emicizumab was started and bleeding had ceased, the previous antiplatelet therapy was resumed. At 7 days, because of an increase in inhibitor titer (58 BU) and because the patient was elderly, the corticosteroid was discontinued and anti-CD20 therapy, rituximab, was started at 375 mg/m^2/week for 4 weeks. The autoimmune profile showed positivity for anti-dsDNA antibodies (25.00 IU/mL), ANA (titer 1/80, homogeneous pattern AC-1), borderline antinucleosome antibodies, anticardiolipin IgM antibodies (11.8 uMPL/mL), and positive anti-beta-2 glycoprotein I IgM antibodies (12.10 U/mL). Serology for hepatotropic viruses tested negative.

Despite treatment, the inhibitor titer peaked on day +14 (91 BU), indicating poor prognosis (> 20 BU). After the start of emicizumab, no further bleeding occurred. The patient was discharged with outpatient hematology follow-up. As an intercurrent event, he attended the Emergency Department because of head trauma with a hematoma in the right supraciliary region and was treated with one dose of rFVIIa 90 μg/kg while awaiting the result of cranial computed tomography (CT), which showed no abnormalities. He had no other bleeding events. The inhibitor progressively decreased, reaching complete remission on day +60 (Fig. 2). At that time, emicizumab prophylaxis was discontinued, with initially weekly monitoring during the first month and progressive spacing thereafter, once the risk of relapse ranged from 12–18% depending on the initial regimen,[2] and was lower with anti-CD20 therapy. Controls have remained persistently negative, with inhibitor titer < 0.4 BU.

Discussion

AHA is a rare but potentially serious coagulopathy characterized by the sudden appearance of autoantibodies against FVIII, which is associated with severe bleeding and high morbidity and mortality, especially in elderly patients with comorbidities,[1-3,11] such as the patient presented here. Our case illustrates the early use of emicizumab as prophylaxis after initial bleeding control with rFVIIa in a frail patient with active cancer.

This strategy is consistent with evidence from prospective studies such as GTH-AHA-EMI and AGEHA, in which emicizumab significantly reduced the incidence rate of new clinically relevant bleeding events

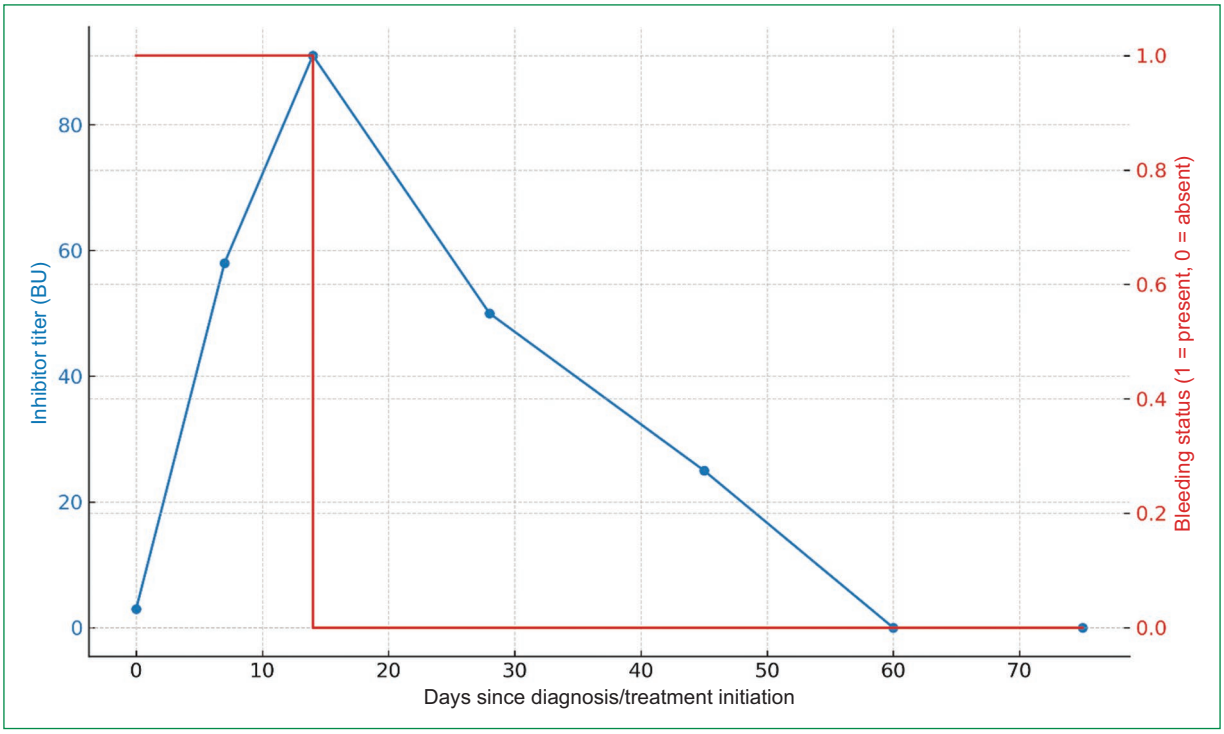


Figure 2. Evolution of inhibitor titer and bleeding in the patient.*
*Active bleeding is represented as 1 and absence of bleeding as 0. The inhibitor peaked on day +14 and remission was achieved on day +60.

and allowed IS to be deferred or even avoided in a substantial proportion of patients.[7,10] In the GTH-AHA-EMI study, 75% of patients remained free from bleeding within the first 12 weeks without initial IS,[7] whereas AGEHA documented the absence of major bleeding in both cohorts, even in patients without IS.[10] In our case, emicizumab prevented hemorrhagic recurrence despite inhibitor titers as high as 91 BU and allowed reintroduction of the previous antiplatelet therapy without complications, findings consistent with recent series.[12,13]

In addition, the time to complete remission, 60 days, was comparable to that reported in the Spanish registry, median 49 days; IQR, 34–89,[3] and somewhat shorter than that observed in the GTH-AH 01/2010 registry, 79 days; IQR, 48–102,[4] despite a more conservative IS strategy based on rituximab monotherapy. This reinforces the hypothesis that prophylaxis with emicizumab provides a "safety window" that makes it possible to reduce the intensity of IS, minimizing toxicity without compromising efficacy.

Of note, the conditions frequently associated with the development of AHA, such as advanced age, pregnancy and the puerperium, and cancer, are characterized per se by a higher baseline thrombotic risk,[1,4] which should be taken into consideration when initiating treatment with emicizumab. This drug may increase the risk of thrombosis in patients with AHA, especially when endogenous FVIII levels rise as a result of effective IS therapy, creating a state of relative hypercoagulability. In the present case, positivity for anticardiolipin IgM and anti-beta-2 glycoprotein I IgM added an additional thrombotic risk that justified close monitoring. Therefore, strict follow-up is recommended to detect thrombotic events early, such as deep vein thrombosis or stroke, especially in patients with preexisting cardiovascular risk factors.[11,12] Once endogenous FVIII values reach or exceed 50%, treatment with emicizumab should be discontinued to prevent thrombosis.[6,12]

In terms of overall safety, our patient tolerated treatment without relevant incidents, thrombotic events, or serious infections. The thrombotic risk described in the literature is mainly associated with the concomitant use of high-dose aPCC along with emicizumab,[5,6] which reinforces the recommendation to prioritize rFVIIa or recombinant porcine FVIII in acute bleeding in patients receiving prophylaxis with emicizumab, avoiding aPCC in this context.[6,11]

This approach raises several considerations. First, the current evidence comes from nonrandomized studies with small samples. Although the results are consistent, generalization requires caution. Second, the use of emicizumab in AHA is off-label in most countries, except Japan. This requires individualized indication supported by sound clinical and ethical criteria. Third, the optimal timing of initiation and the combination with IS have not yet been agreed upon. Studies such as AGEHA and GTH-AHA-EMI provide criteria, but formal guidelines integrating this strategy are still lacking.[7,10]

In conclusion, this case supports the evidence backing the use of emicizumab as hemostatic treatment in acquired hemophilia A, especially in frail patients or those at high risk of complications derived from IS. Its ability to prevent new bleeding events, reduce the use of bypassing agents, and allow delayed initiation of IS could represent a paradigm shift in the initial management of this condition. Larger controlled clinical trials are required to confirm these findings and define standardized protocols.

Funding

This study received no specific funding from public-sector agencies, the commercial sector, or nonprofit organizations.

Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

Protection of humans 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 followed the protocols of their healthcare center/institution for access to data from medical records. Informed consent was obtained from the patients, and approval from the Ethics Committee was obtained. The recommendations of the SAGER guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that ChatGPT-5 was used to create figure 1.

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Endovascular intervention for intracranial aneurysm with dual anti platelet therapy in a patient with severe hemophilia A

Intervención endovascular de un aneurisma intracraneal con terapia antiplaquetaria dual en un paciente con hemofilia A grave

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We describe the case of a 41-year-old man with severe haemophilia A without inhibitors, who presented with mild headache and blurred vision.

The patient was referred to a neurologist, who requested cerebral magnetic resonance angiography, which revealed a 4.5-mm ophthalmic artery aneurysm. An endovascular stent placement by interventional radiology and dual antiplatelet therapy were proposed.

The patient was receiving tertiary prophylaxis with a standard half-life recombinant factor VIII. Despite his severe arthropathy, he had a very active lifestyle, performing regular training that combined muscle strength training and CrossFit sessions.

Given his bleeding disorder and the additional bleeding risk associated with dual antiplatelet therapy to prevent stent occlusion, and because there are no specific recommendations regarding FVIII levels for this clinical scenario, we decided to follow adaptations of the European Society of Cardiology recommendations on the management of acute coronary syndromes in patients with haemophilia.[1]

He was switched to a pegylated extended half-life recombinant factor VIII (EHL), targeting a trough level between 20 and 30%. A dose of 3,500 IU (44.8 IU/kg; patient weight, 78 kg) twice weekly was calculated with the aid of the WAPPS HEMO tool. Pharmacokinetic assessment was performed after the switch, confirming a trough level of 22% for 91% of the time and an area under the curve of 4,230 IU/h/dL. Dual antiplatelet therapy was started 7 days before stent placement and maintained for 4 months thereafter.

The patient experienced 2 spontaneous bleeding episodes: haemarthrosis of the left elbow (a joint with arthropathy), treated with 4 additional daily doses of FVIII in addition to regular prophylaxis, and haemarthrosis of the right knee (a joint with arthropathy), which resolved 48 h after receiving 2 additional doses of EHL FVIII.

After the initial 4 months of dual antiplatelet therapy, following a new dose adjustment with the aid of WAPPS HEMO to 2,500 IU twice weekly (44.6 IU/kg; patient weight, 56 kg), he remained at a trough level between 10 and 15% during the year on single antiplatelet therapy

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Date of reception: 03-12-2025
Date of acceptance: 15-06-2026
DOI: 10.24875/RHT.M26000093

Available online: 03-09-2026
Hemost Trombos (Eng). 2026;3(2):79-80
www.revistahemostasiaytrombosis.com

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with acetylsalicylic acid, with no bleeding episodes during that period.

Discussion

Severe factor VIII deficiency poses an increased risk of joint bleeding and bleeding from other sites. This is partially prevented with contemporary prophylactic treatment, which achieves minimum levels around or above 1 IU/dL, thereby converting the severe phenotype into a moderate one.[2] However, the appropriate minimum level needed to prevent bleeding in patients with additional bleeding risks, for example, in patients requiring antiplatelet or anticoagulant therapy, is not well established.[3]

Data are scarce, although clinical practice guidelines exist for the treatment and management of coronary syndromes that are extrapolated to patients with haemophilia, providing advice on minimum factor levels that are sufficiently safe to allow the use of antiplatelet therapies, anticoagulants, or both, to prevent spontaneous bleeding.[1] While these guidelines focus on myocardial infarction, atrial fibrillation, and other related comorbidities, they do not address cerebral aneurysm.

Taken together, these clinical scenarios represent a major challenge for physicians and require discussion and management by a comprehensive team including a haematologist experienced in haemophilia, a neurologist, an intensive care provider, and an interventional radiologist.

The clinical outcome in our patient was satisfactory, with no major breakthrough life-threatening bleeding, supporting the idea that, regardless of the underlying condition for which dual antiplatelet therapy is indicated, an FVIII level of 20–30% appears to be safe to cover the bleeding risk associated with dual antiplatelet therapy, according to adaptations of the European guideline recommendations.

We decided to switch the patient to an extended half-life product given the higher minimum level that could be achieved with twice-weekly administration.

Conclusions

Further information on the management of cerebrovascular and cardiovascular diseases in patients with haemophilia will be required in the near future, given that this is an ageing population and an increase in these comorbidities is expected.

Acknowledgements

We would like to thank all patients with haemophilia treated at *Medicarte* for their trust in us. We acknowledge the combined efforts of the interventional radiology team, who were receptive to our recommendations and worked as a team with our department.

Funding

This study received no specific funding from public-sector agencies, the commercial sector, or non-profit organisations.

Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The authors obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymised clinical data; therefore, informed consent was not required. The relevant recommendations were followed.

Declaration on the use of artificial intelligence. The authors declare that they did not use any form of generative artificial intelligence in the writing of this manuscript.

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