Hemostasia y Trombosis
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REVIEW ARTICLE

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

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

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Abstract

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

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

Resumen

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

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Date of reception: 17-07-2024
Date of acceptance: 24-07-2024
DOI: 10.24875/RHT.M24000010

Available online: 04-05-2026
Hemost Trombos (Eng). 2026;3(1):21-28
www.revistahemostasiaytrombosis.com

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

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

Introduction

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

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

Prophylaxis

Which patients should receive prophylaxis?

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

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

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

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

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

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

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

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

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

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

What should be the aim of prophylaxis?

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

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

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

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

Recombinant FVIII prophylaxis: beyond pharmacokinetics (PKs)

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

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

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

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

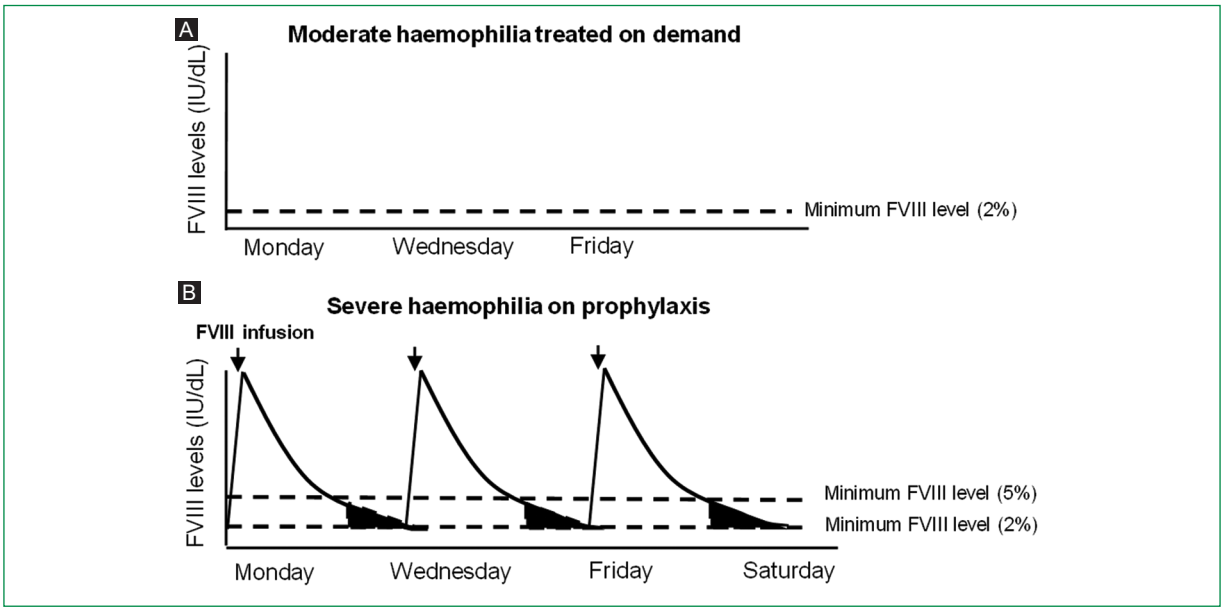

Figure 1. Schematic representation of the time spent at different clotting factor levels comparing **A:** moderate hemophilia treated episodically. In moderate hemophilia, the baseline level of factor VIII (FVIII) is consistently low throughout the week with no peaks of FVIII/FIX at the time of potential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

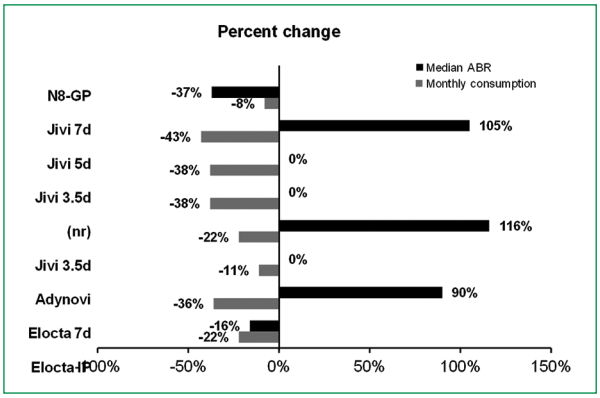

Figure 2. Percentage changes in monthly concentrate consumption and ABR for several EHF factor VIII concentrates as compared with octocog alfa (Advate®) in a PK-guided prophylaxis regimen. ABR: annualized bleeding rate; d: days; IP: individualized prophylaxis; nr: patients receiving BAY-94 9027 with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

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

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

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

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

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

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

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

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

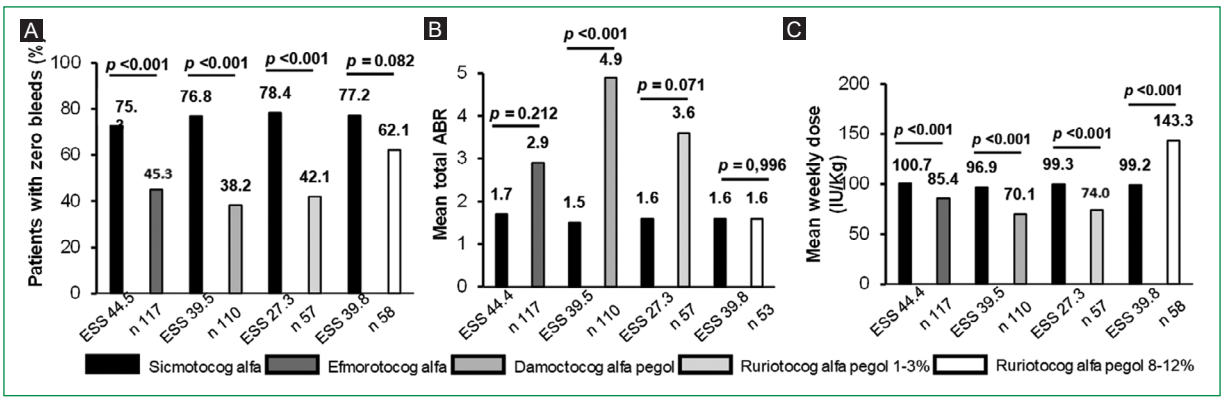

Figure 3. Matching-adjusted indirect comparison of simoctocog alfa *versus* efmoroctocog alfa, damoctocog alfa, and rurioctocog alfa *(adapted from Kessler et al.).*[25] The ESS for simoctocog alfa after matching the populations based on baseline characteristics were 44.4, 39.5, 27.3, and 39.8 for the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

Conclusions

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

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

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

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

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

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

Acknowledgments

The authors acknowledge the medical writing support provided by Susana Cañón, PhD (Medical Statistics Consulting, S.L., Valencia, Spain).

Funding

None.

Conflicts of interests

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

Ethical considerations

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

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

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

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