

# Switching to extended half-life factor VIII concentrates or non-factor replacement therapies in patients with severe-to-moderate haemophilia A without inhibition: retrospective analysis. Experience of the Galician Thrombosis and Hemostasis Working Group (G2TH-AGHH)

## Cambio a concentrados de factor VIII de vida media prolongada o terapias no sustitutivas en pacientes con hemofilia A grave o moderada sin inhibidor: análisis retrospectivo. Experiencia del Grupo Gallego de Trombosis y Hemostasia (G2TH-AGHH)

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### Abstract

**Introduction:** The concept of prophylaxis in hemophilia has changed significantly due to the shift from standard half-life (SHL) to extended half-life (EHL) factor VIII concentrates and the emergence of the subcutaneous administration of emicizumab. **Objective:** To report the experience and results of prophylaxis in patients with moderate-to-severe hemophilia A in Galicia, Spain after switching from SHL-CF8 to EHL-CF8 or emicizumab. **Methods:** Retrospective study of patients with severe-to-moderate hemophilia A without inhibition who switched from SHL-CF8 to EHL-CF8 or emicizumab in Galicia until December 2023. The analysis covers the 12 months prior and 12 months following the switch, and the last 12 months after the switch. Data were collected from patients' electronic health records. **Results:** a total of 27 men were included, with a median age of 29.5 years (range, 5-57) and prior SHL-CF8 prophylaxis. Median F8 consumption changed from 312,000 IU/year for SHL-CF8 to 266,875 IU/year for EHL-CF8, with a decrease in the median number of weekly infusions from 3 down to 1.875 and an increase in the trough F8:C level from 1.67 up to 3.8 IU/dL. The mean bleeds (annualized bleeding rate [ABR]) occurred in the period of SHL-CF8 use was 2.33, vs 0.83 with EHL-CF8, dropping down to 0.3 over the past 12 months ( $p < 0.0028$  and  $p < 0.0002$ , respectively). The mean spontaneous ABR was 0.45, 0.33 and 0.1 respectively, and the joint ABR dropped from 1.66 down to 0.66 and 0.13 after the switch. Arthropathy was described in 42.31% and 36.36% after the switch and over the past 12 months, respectively. In addition, 4 patients switched to emicizumab, with a reduction in the total mean number of ABR from 1.5 down to 0 and spontaneous ABR from 0.25 down to 0, while joint ABR did not change (0 to 0) regardless of the frequency of emicizumab prophylaxis. The main reasons for the switch were reduction in the number of infusions and prevention of bleeding (15.38% each). The HEAD-US (Hemophilia Early Arthropathy Detection with Ultrasound) evaluation was not performed because it was not implemented in all centers. **Conclusions:** Overall, the results show an improved clinical profile for the patients who switched to the EHL product and, as result, an increased minimum

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through level, with lower consumption of the factor and reduction of treatment burden, which is consistent with clinical trials and the real-work experience reported by other groups.

**Keywords:** Hemophilia A. Switch. Prophylaxis. Non-factor replacement therapies.

## Resumen

**Introducción:** El concepto de profilaxis en hemofilia ha cambiado significativamente gracias al cambio de concentrados de factor VIII de vida media estándar (SHL, standard half life) a vida media prolongada (EHL, extended half life), y a la aparición del emicizumab, de administración subcutánea. **Objetivo:** Reportar la experiencia y los resultados de la profilaxis en pacientes con hemofilia A moderada/grave en Galicia, tras el cambio de SHL-CF8 a EHL-CF8 o emicizumab. **Método:** Estudio retrospectivo en pacientes con hemofilia A grave o moderada sin inhibidor, que cambiaron de SHL-CF8 a EHL-CF8 o emicizumab en Galicia hasta diciembre de 2023. El análisis abarca los 12 meses anteriores y los 12 meses posteriores al cambio, así como los últimos 12 meses. Los datos se recopilaron de las historias clínicas electrónicas de los pacientes. **Resultados:** Se incluyeron 27 varones, con una mediana de edad de 29,5 años (rango: 5-57) y profilaxis previa con SHL-CF8. La mediana de consumo de F8 pasó de 312.000 UI/año para SHL-CF8 a 266.875 UI/año para EHL-CF8, con un descenso de la mediana de infusiones semanales de 3 a 1,875 y un aumento del nivel valle de F8:C de 1,67 a 3,8 UI/dl. El promedio de sangrados (tasa anualizada de sangrado [TAS]) en el periodo de uso de SHL-CF8 fue de 2,33, frente a 0,83 con EHL-CF8, descendiendo a 0,3 en los últimos 12 meses ( $p < 0,0028$  y  $p < 0,0002$ , respectivamente). La TAS espontánea media fue de 0,45, 0,33 y 0,1 respectivamente, y la TAS articular pasó de 1,66 a 0,66 y 0,13 tras el cambio. Se describió artropatía en el 42,31% y el 36,36% tras el cambio y en los últimos 12 meses, respectivamente. Además, cuatro pacientes efectuaron el cambio a emicizumab, con una reducción de la media de la TAS total de 1,5 a 0 y espontánea de 0,25 a 0, mientras que la articular no varió (0 y 0), con independencia de la frecuencia de la profilaxis con emicizumab. Las principales razones para el cambio de producto fueron la reducción del número de infusiones y la prevención del sangrado (15,38% cada una). No se efectuó la evaluación HEAD-US (Hemophilia Early Arthropathy Detection with Ultrasound) por no estar implementada de forma sistemática en todos los centros. **Conclusiones:** Globalmente, los resultados ponen de manifiesto una mejoría del perfil clínico de los pacientes por el producto EHL y por el aumento del nivel valle mínimo del factor, con menor consumo del mismo y reducción de la carga asociada al tratamiento, en consonancia con lo descrito en ensayos clínicos y con la experiencia reportada por otros grupos en la vida real.

**Palabras clave:** Hemofilia A. Cambio. Profilaxis. Terapias no sustitutivas.

## Introduction

Currently, for patients with severe phenotypes of hemophilia A or B, the World Federation of Hemophilia recommends that they should receive sufficient prophylaxis to prevent bleeding at all times. However, this prophylaxis should be individualized, considering the patient's bleeding phenotype, joint status, personal pharmacokinetics, and self-assessment and preferences<sup>1</sup>.

The concept of prophylaxis in hemophilia has dramatically changed due to the shift from standard half-life (SHL) concentrates to extended half-life (EHL) concentrates and the introduction of subcutaneously administered emicizumab. These advancements have shown beneficial effects by overcoming the classical limitations of prophylaxis, such as reducing the frequency of infusions or eliminating them completely, maintaining a higher minimum or trough level<sup>2,3</sup> to guarantee a lower risk of bleeding, and making treatment significantly less distressing for patients by improving quality of life by reducing or avoiding IV administration, confirming the results observed in clinical trials<sup>2,3</sup>.

Typically, hemophilia is characterized by spontaneous bleeding episodes in the most severe cases, or is due to trauma. These repeated bleedings, when affecting the joints, eventually cause joint damage and, consequently, chronic arthropathy with compromised joint mobility<sup>4,5</sup>. Although prophylaxis with standard half-life factor VIII concentrates (SHL-CF8) has proven effective in preventing joint damage and reducing the frequency of bleeds, it does not guarantee an overall protection. Moreover, prophylaxis protocols with these products require recurrent venipuncture (2-3 times/week), which is one of the main reasons for lack of adherence, especially in children and adolescents<sup>1,2</sup>.

The half-life extension of recombinant products stimulates adherence by reducing the frequency of infusions (estimated at 30% up to 35%) and increasing protection against bleeding by raising the trough level (approximately 3%)<sup>6-9</sup>. On the other hand, subcutaneously administered emicizumab, in various prophylactic regimens (weekly, bi-weekly, or monthly), has shown not only efficacy but also a great capacity to increase patient adherence to treatment<sup>10,11</sup>.

The objective of this study was to report the experience and results of prophylaxis in patients with moderate-to-severe hemophilia A in Galicia, Spain after switching from SHL-CF8 to EHL-CF8 or emicizumab, by evaluating annualized bleeding rates (ABR), protection, and treatment-associated burden, comparing these results with data reported in the scientific literature.

## Method

We conducted a retrospective study of patients with severe or moderate hemophilia A without inhibitors, who switched from SHL-CF8 to EHL-CF8 or emicizumab in Galicia, Spain until December 2023, including patients of all ages, treated at the hematology services of 5 hospitals within the Sergas (Servizo Galego de Saúde) network, all of which are tertiary referral centers. None of these hospitals are CSUR (Service Centers and Reference Units) for congenital coagulopathies nor do they meet the criteria defined by the Spanish Ministry of Health and Consumer Affairs to be considered comprehensive care and treatment centers for the management of hemophilia.

The analysis covers the 12 months prior and the 12 months following the switch, as well as the last 12 months. Data were collected from the patients' electronic health records. The analysis period was 36 months. Factor VIII level determination was conducted using the 1-stage clotting method.

Statistical analysis of data was performed using Stata 14 software. The following procedures were conducted:

- Data import: from an Excel file using the Stata command `import excel`, making sure that the first row contained the variable names.
- Normality tests: the Shapiro-Wilk test was used to assess the normality of the distributions of continuous variables, such as age, baseline factor VIII level (NIVELBASALF8C), and annual factor consumption, among others.
- Descriptive statistics: detailed descriptive statistics (summarize, detail) were generated for each variable of interest, providing measures of central tendency (mean, median) and dispersion (standard deviation [SD], interquartile range [IQR]).
- Generation and transformation of variables: new variables were created from existing ones to facilitate analysis. For example, the variable NIVELBASALF8C was generated to classify baseline factor VIII level into severe ( $\leq 1$ ) and moderate ( $> 1$ ) categories, using the `generate` and `cond` commands.

- Value labeling: labels were defined and assigned to categorical variables to improve result interpretation. For example, the mutation type variable was labeled with descriptive values (label define and label values).
- Frequency tabulation: frequency tabulations (`tabulate`) were conducted for categorical variables, such as treatment type, previous product, and reasons for treatment change, to evaluate the distribution of these categories in the sample.
- Regimen and annual consumption analysis: dosing regimens and annual factor consumption were analyzed using detailed descriptive statistics and normality tests. Variables included in this analysis were dosing regimen, annual factor consumption, and frequency of weekly infusions.
- ABR evaluation: total and spontaneous ABR were evaluated using normality tests and detailed descriptive statistics for the variables total ABR, joint ABR, total-EHL ABR, and spontaneous-EHL ABR. The Wilcoxon test was applied to check for statistical significance. For total ABR, the Wilcoxon test was used to check for statistically significant differences between values before and after the treatment switch.
- Conditional analysis: conditional analyses were conducted to evaluate regimens and consumption without treatment with emicizumab, preserving and restoring the data set status as needed.
- Reasons for treatment change: reasons for treatment change were labeled and tabulated to understand the clinical decision-making process within the studied sample.

## Results

The study included a total of 26 men with a median age of 29.5 years (range, 5-57), all previously on SHL-CF8 prophylaxis, except for 4 who were previously on demand treatment. All patients, except for 6, were diagnosed with severe hemophilia A ( $F8:C \leq 1\%$ ). Forty percent of all patients on previous prophylaxis ( $n = 22$ ) were on primary prophylaxis, 20% on secondary prophylaxis, and 40% on tertiary prophylaxis. Baseline characteristics of the patients are shown in [table 1](#). [Figure 1](#) shows the type of factor and the switch.

Regarding consumption, the median was 312,000 IU/year (IQR, 260,000-410,625) for SHL-CF8 and 266,875 IU/year (IQR, 220,000-312,000) for EHL-CF8, with a median of 3 infusions/week (IQR, 3-3.5) and 1.875 infusions per week (IQR, 1.4-2.33), respectively, estimating a 37.5% reduction. The trough level of F8 obtained with SHL-CF8 averaged 1.67 IU/dL

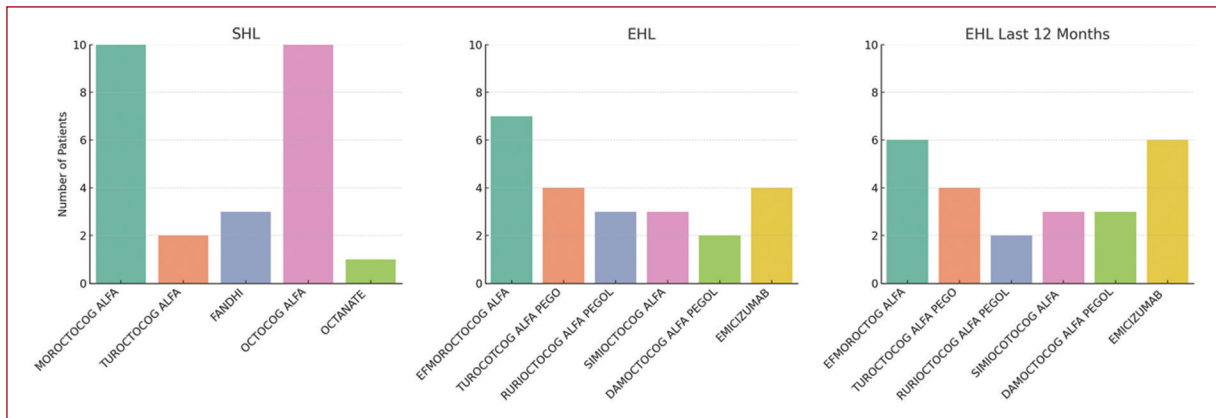


**Figure 1.** Description of treatments used before and after switching products.

**Table 1.** General characteristics of the study population

|                                          |                |
|------------------------------------------|----------------|
| Age, years, median (IQR)                 | 29.5 (18-42)   |
| Baseline F8 level, mean (SD)             | 1.12 (1.21)    |
| Type of hemophilia A                     |                |
| Mild                                     | 0/26           |
| Moderate                                 | 6/26 (23.08%)  |
| Severe                                   | 20/26 (76.92%) |
| Genetics                                 |                |
| Intron 22 inversion                      | 15/26 (57.89%) |
| Missense mutation                        | 7/26 (26.92%)  |
| Intron 1 inversion                       | 1/26 (3.84%)   |
| Unknown                                  | 2/26 (7.69%)   |
| Type of treatment                        |                |
| Prophylaxis                              | 22/26 (84.62%) |
| On demand                                | 4/26 (15.38%)  |
| Reasons for the switch                   |                |
| Increase in trough level                 | 3/26 (11.54%)  |
| Fewer infusions                          | 4/26 (15.38%)  |
| Bleeding prevention                      | 4/26 (15.38%)  |
| Intolerance to IV route                  | 3/26 (11.54%)  |
| Reduction in treatment-associated burden | 2/26 (7.69%)   |
| Improve adherence                        | 1/26 (3.84%)   |
| History of anti-FVIII inhibition         | 1/26 (3.84%)   |

SD: standard deviation; IQR: interquartile range.

**Table 2.** Factor VIII consumption, weekly infusion frequency, and trough level before and after treatment switch

|                                      | SHL-CF8 | EHL-CF8 |
|--------------------------------------|---------|---------|
| Annual F8 consumption (IU), median   | 312,000 | 266,875 |
| Number of infusions per week, median | 3       | 1.875   |
| Trough level of F8 (IU/dL), median   | 1.67    | 3.8     |
| Anti-FVIII inhibitors                | 0       | 0       |

**Table 3.** Bleeding pattern before and after treatment switch

|                       | SHL-CF8 | EHL-CF8<br>First 12<br>Months | EHL-CF8<br>Last 12<br>Months |
|-----------------------|---------|-------------------------------|------------------------------|
| Total ABR, mean       | 2.33    | 0.83                          | 0.30                         |
| Spontaneous ABR, mean | 0.45    | 0.33                          | 0.10                         |
| Joint ABR, mean       | 1.66    | 0.66                          | 0.13                         |

ABR: annualized bleeding rate.

(SD, 1.14), vs 3.8 IU/dL (SD, 2.81) with EHL-CF8 ( $p = 0.034$ ) (Table 2). The mean number of bleeds (ABR) during the SHL-CF8 period was 2.33 (SD, 2.99) vs 0.83 (SD, 0.76) with EHL-CF8 dropping down to 0.3 (SD, 0.47) over the past 12 months ( $p < 0.0028$  and  $p < 0.0002$ , respectively), with a 64.28% reduction in bleeds at the 12-month follow-up following the switch and 87.5% over the past 12 months of analysis. Similarly, the mean spontaneous ABR recorded was 0.45 (SD, 1.02), 0.33 (SD, 0.7), and 0.1 (SD, 0.28), respectively, with a 27.27% decrease within the first 12 months after

the switch, increasing up to 81.81% over the past 12 months. The joint ABR was 1.66 (SD, 2.39) with SHL-CF8, dropping down to 0.66 (SD, 0.76) within the first 12 months after switching to EHL-CF8 and to 0.13 (SD, 0.34) over the past 12 months, representing a 60% and 92.5% reduction, respectively (Table 2). Arthropathy was present in 42.31% before the change to EHL and 36.36% over the last 12 months (Table 3).

The series includes 4 patients diagnosed with severe hemophilia A, 2 pediatric and 2 adult patients, with a mean age of 19.5 years (range 5-34), and the 2 adults

had arthropathy. All 4 switched from SHL-CF8 to emicizumab. Prior to the switch, the mean total ABR was 1.5 (0-4), the spontaneous ABR was 0.25 (0-1), and the joint ABR was 0. After switching to emicizumab, whether bi-weekly (50%) or monthly (50%), all ABRs averaged 0. Over the past 12 months of analysis, the 2 patients on bi-weekly prophylaxis switched to monthly regimens to reduce costs, and in all 4 patients, the total, spontaneous, and joint ABRs remained at 0.

The main reasons for the switch were fewer number of infusions and bleeding prevention (15.38% each), followed by the increase in the trough level of F8, and avoiding the need for IV administration (11.54% each) (Table 1). The HEAD-US evaluation (Hemophilia Early Arthropathy Detection with Ultrasound) was not performed as it is not systematically implemented in all centers.

## Discussion and conclusions

It is accepted that prophylaxis with EHL-CF8 or emicizumab increases protection against bleeding, especially spontaneous bleeding, reduces the treatment burden<sup>1</sup>, and possibly improves therapeutic adherence. Overall, our results highlight these changes. An improvement in the clinical profile of patients is observed, not only due to the EHL product but also due to the increased trough level. Additionally, these objectives are achieved with lower factor consumption and reduced treatment burden, which is consistent with clinical trial descriptions and real-world experiences reported by other groups. In the study by Peyvandi et al.<sup>2</sup>, results reported that 33 hemophilia treatment centers that responded to the European Association of Haemophilia and Allied Disorders (EAHAD) survey showed a beneficial effect of EHL-CF8 products in reducing the number of infusions by  $\geq 30\%$  in 66% of the centers. Our results show a 37.5% reduction, which is consistent with what was reported by Peyvandi et al.<sup>2</sup> in their study. We observed a 56.06% increase in the trough level, which is consistent with the EAHAD survey findings, which reported a 3% up to 5% increase in the trough level of 67% of patients. Regarding efficacy, our data indicate a 65.67% reduction in total ABR within the first 12 months after the switch, increasing up to 87.13% in the last 12 months of analysis, while it was  $\leq 50\%$  in 86% (18/21) of the centers that responded to the EAHAD survey. This difference may be due to various factors, such as the patients' bleeding phenotype, the baseline joint status before the switch, or the observation period, among others. In the EAHAD

survey, the number of patients who switched to EHL drugs was low; approximately 72% of the centers had switched  $< 10\%$  of their patients with hemophilia A, whereas in our case, the results correspond to the switch in 100% of the patients, a fact that could also justify the differences observed in the results obtained.

Other real-world experiences confirm the findings of our work, namely, that treatment with EHL-CF8 reduces the number of infusions by 30% up to 40% with a substantially lower ABR in patients on prophylaxis vs on-demand treatment. In 2022, Nummi et al.<sup>12</sup> compared clinical and laboratory results between prophylaxis with SHL-CF8 and EHL-CF8 in patients who switched products, including 38 patients with a median age of 38 years (range, 17-75), slightly higher than our series (29.5 years; range, 5-57), and after the switch, weekly infusions decreased by a median of 29% (37.5% in our series). The number of infusions per week decreased from 2.8 down to 2.0, while in the Galician series it decreased from 3 down to 1.875. At the same time, factor consumption for prophylaxis decreased by 17%, vs 14.47% in the Galician series. Factor VIII use decreased in 55% of patients, reaching 100% in our series after the switch. In our series, total ABR remained low (2.33 for SHL-CF8 and 0.33 for EHL-CF8), which is similar to what was reported by Nummi et al.<sup>12</sup> (1.0 for SHL and 0.5 for EHL-CF8).

In 2023, Blatny et al.<sup>13</sup> reported the real-world experience with efmoctocog alfa by analyzing 46 eligible publications (8 full-text articles) and concluded that this EHL-CF8 showed a low ABR. Studies evaluating the switch from SHL-CF8 to efmoctocog alfa found a reduction in ABR, with a median between 0 and 2; in our series, in 7 patients who switched to efmoctocog alfa, the median ABR was also between 0 and 2, dropping down to 0 over the past 12 months of analysis. Additionally, the median number of injections per week ranged from 1.8 up to 2.4, and in our series, it ranged from 1.17 up to 2.33, remaining constant in the different periods analyzed. Therefore, despite the limitations of the small sample size, our data are consistent with the literature, reflecting the improvement in the benefit associated with prophylaxis over time, as shown in Table 2.

In that same year, George et al.<sup>14</sup> reported the Australian experience of switching to EHL-CF in hemophilia patients, including 115 patients with hemophilia A. Of these, 63.5% reported 0 spontaneous bleeds over 12 months. In our experience, the patients without spontaneous bleeds were 75% within the first 12 months after the switch and 87.5% within the last 12 months. However, this data also depends on various factors,

such as the prophylaxis regimen used (dose/frequency), lifestyle, and the joint status of the patient, among others.

Regarding patients who switched to emicizumab, the results show a reduction in ABR and clinical improvement, which is consistent with what has been reported in clinical trials<sup>10,11</sup> and real-world studies<sup>15,16</sup>, although some skepticism remains about the potential benefit of this switch. In the study by Levy-Mendelovich et al.<sup>15</sup> of 70 patients with hemophilia A (aged 1 month to 79 years), the risk of bleeding persisted despite treatment, especially in patients with problematic joints and target joints, children who suffer trauma-related bleeds, and elderly patients. Meanwhile, in the study by Escobar et al.<sup>16</sup>, which included 131 patients with a total of 82 and 45 bleeds in the pre- and post-switch periods, respectively, with a mean follow-up before the switch of 978.37 days (SD, 555.03) and post-switch of 522.26 days (SD, 191.36), no significant differences were observed in the mean ABR before and after the switch (0.25 and 0.20, respectively;  $p = 0.4456$ ). The authors concluded that the switch to emicizumab may not provide additional benefits for hemophilia patients on prophylaxis. In our series, with far fewer patients and a shorter follow-up period, the results are excellent: the total, spontaneous, and joint ABR averages are 0 with the monthly regimens. This contrasts with the reported monthly prophylaxis regimen in clinical trials<sup>11</sup>, with an average treated bleed ABR of 2.4 (1.4-4.3), a spontaneous treated ABR of 0.6 (0.3-1.5), and a joint treated ABR of 1.7 (0.8-3.7). Nevertheless, these analyses<sup>14,15</sup>, in our opinion, should be considered when selecting candidates for subcutaneous prophylaxis to maximize the efficiency of our resources through the much-needed personalization in the selection of both the patient and the product (even if it is emicizumab) and the administration regimen.

Additionally, in our series, no development of inhibitors was reported after treatment switch. This is expected given the low risk of this complication reported in the literature related to product switching (0.1-0.6% per patient/year<sup>17</sup>). Of note that 1 of the patients who switched to EHL-CF8 (in this case, to rurioctocog alfa pegol) had a history of an inhibitor developed 10 years ago with octocog alfa, successfully eradicated, and on prophylaxis with octocog alfa 3 times a week. Although patients with a history of inhibitors were excluded from the clinical development of rurioctocog alfa pegol<sup>18</sup>, we proceeded with the product switch to increase trough levels and reduce treatment burden. The switch was not associated with a reappearance of neutralizing

antibodies against factor VIII. Besides the almost 30% reduction in the infusion regimen, the clinical and ultrasound findings consistent with synovitis in the right ankle disappeared. This improvement is likely associated with the increase in trough levels (from 1 up to 3 IU/dL) and the rehabilitation program undertaken.

Finally, most patients have expressed satisfaction with the treatment with EHL-CF8 or emicizumab, as the reduced infusion frequency or absence of IV use has led to greater independence concerning their disease and a reduced treatment burden, especially due to venipuncture. On the other hand, when the objective of the switch was not to reduce infusion frequency but increase trough levels for better bleed protection, as seen by the reduction in total, spontaneous, and joint ABR, the expectations of both patients and clinicians regarding these drugs have been met. This is consistent with the World Federation of Hemophilia guidelines<sup>1</sup> and real-world studies, such as the HOPE trial<sup>19</sup>. The switch also reduces the workload associated with fewer visits to the ER for intercurrent bleeds. Clinical results are consistent with similar, larger-scale experiences published in the literature, without significant safety issues, and no reports of inhibitor development against factor VIII.

It is true that among the limitations of this work, in addition to the small sample size and its retrospective nature, is the lack of widespread implementation of joint evaluation using the HEAD-US, which would allow for objective advantages derived from the decision to change treatment. Moreover, given the high efficacy of current treatments, which often allow achieving the goal of 0 spontaneous bleeds, it is essential to measure outcomes in hemophilia with other variables such as the HEAD-US. This would further justify to managers and pharmacy services the appropriateness of the change from SHL-CF8 to these products. It is expected that this joint evaluation system will gradually be incorporated into our daily practice and that of radiologists in our centers.

Our results support what is reflected in the literature: switching to prophylaxis with EHL-CF8 or emicizumab reduces the frequency of infusions and improves adherence, providing more stable levels of factor VIII and the convenience of subcutaneous administration, significantly improving the quality of life and reducing bleeding episodes.

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None declared.

## Conflicts of interest

None declared.

## Ethical disclosures

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

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

**Right to privacy and informed consent.** The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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

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