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Original Research

# Cost of patients with hemophilia A treated with standard half-life or extended half-life FVIII in Spain

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A probabilistic model in a 1-year time horizon was used in order to analyze the cost comparison of SHL and EHL rFVIII products in Spain. In this analysis, mean IUs were those of the RWA, and frequency of use and prices for each rFVIII were obtained from sales estimates based on Spanish sources (IQVIA; €, 2019)

## Results

Data showed an average annual savings per patient of €11,227 for SHL rFVIII versus EHL rFVIII products, with a savings probability of 75.5%. The results were stable in the sensitivity analyses. Not switching treatment from SHL to EHL rFVIII resulted in greater savings per patient (€53,078), with a savings probability of 99.9%. Considering the frequency of rFVIII dispensation in the US, annual savings per patient would increase to €16,350 in Spain, with a savings probability of 79.9%.

## Conclusions

According to this model, use of SHL rFVIII versus EHL rFVIII products could lead to savings for the Spanish National Health System.

KEYWORDS: Hemophilia A | recombinant factor VIII | extended half-life | standard half-life | cost comparison

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prevent bleeding events and joint damage should be the main treatment goal, with the aim of preserving normal musculoskeletal function [1].

There are currently two types of rFVIII products, which differ in terms of the pharmacokinetic elimination half-life. Standard half-life (SHL) rFVIII has an elimination half-life of approximately 12 hours, which means that it is administered two to three times per week for prophylaxis [5,6]. Extended half-life (EHL) rFVIII has an elimination half-life ratio of 1.3 or higher than SHL products, which means that it can be administered every 3 to 5 days [7], allowing less frequency of infusions for the patients and the promise of better quality of life. No significant differences have been found in the inhibitor formation rates between the different rFVIII products analyzed globally [8].

In Spain, the first EHL rFVIII was commercially available since October 2016, and since then more EHL have been gradually introduced allowing a broader therapeutic options to hemophilia A patients. Therefore, the following SHL rFVIII products are approved and marketed: lonoctocog alfa [9], moroctocog alfa [10], octocog alfa [11–14], simoctocog alfa [15], and turoctocog alfa [16]. Whilst, the EHL rFVIII products approved and marketed are efmoroctocog alfa [17], rurioctocog alfa pegol [18], damoctocog alfa pegol [19] and turoctocog alfa pegol [20]. The price per IU of rFVIII financed by the Spanish Health System is the same for SHL and EHL products, according to the Reference Price Order [21] established by the Spanish Ministry of Health. Thus, at the same pr

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were limited for the cross-sectional population analysis, but the study included an additional patient-level switch analysis of 29 patients. In the US, pricing of EHL rFVIII products sought parity with SHL rFVIII products by balancing the lower expected need for rFVIII IUs dispensed with a higher per-unit price.

Table 1. Mean IUs of the rFVIII products dispensed quarterly in the US databases and before (pre) and after (post) switching from SHL to EHL [ 6 ]

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Contrary to what was expected from the different dosing guidelines for SHL and EHL products, the median number of IUs of EHL rFVIII products dispensed in clinical practice according to pharmacy claims was 10% higher versus SHL FVIII products for patients in the Optum database, and 45% higher for patients in the Truven database [6].

The objective of this study was to confirm the cost analysis results reported by Chhabra et al. [6]. The research question posed was whether the cost-per-patient was lower with SHL rFVIII than EHL rFVIII replacement products for patients with hemophilia A in Spain.

## 2. Des

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The economic model included the following variables: (1) the mean doses of each rFVIII dispensed (IUs) quarterly, taken from the aforementioned real-world analysis [6] ( Table 1); (2) the frequency of use of each rFVIII product approved in Spain, obtained from a market study dated November 2018 that covered the sales estimations for the previous 12 months in Spain [29] (Table 2); and (3) the frequency of use of each rFVIII product in the United States as reported in the RWA by Chhabra et al. [6] (Table 3).

Table 2. Frequency of use of rFVIII products in a 12 months period (2018) in Spain [ 7 , 29 ]

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Table 3. Frequency of use of rFVIII in the US databases [ 6 ]

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The cost per IU (€0.59 for all of the rFVIII products with publicly financed) was analyzed based on the reported wholesale price for the drugs in Spain, according to the Referenc

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In the different scenarios analyzed, the annual mean savings per HA patients treated with SHL vs. EHL rFVIII products represent a significant probability of savings, as detailed below.

## 3.1. Base case: frequency of use of rFVIII in Spain

In the base case, the mean annual savings for each HA patient treated with an SHL product was €11,227 compared with those who received an EHL product, with a savings probability of 75.5% (Table 4).

Table 4. Mean annual costs (± SD) per patient with hemophilia A treated with SHL or EHL rVIII products, and savings probability with the use of SHL rFVIII products

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## 3.2. Sensitivity analysis 1: considering the frequency of use of rFVIII in the United States

In this case, the annual mean savings per HA patient treated with an SHL versus an EHL product

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According to our probabilistic model, the use of SHL rFVIII products rather than EHL rFVIII products could lead to savings for the Spanish National Health System. The modeling of a hypothetical cohort of 1,000 Spanish patients with hemophilia A treated with a SHL or EHL rFVIII product allowed us, first, to explore the uncertainty of the model's variables, and, second, to calculate the probability of potential savings in patients treated with SHL rFVIII products compared with EHL rFVIII products [23].

Consistent with these results, the RWA conducted in the United States [6] also found higher costs for patients treated with an EHL versus a SHL product. Similar findings were observed in another real-world study with 34 HA patients who switched from a SHL to an EHL product, with mean SHL units of 115,424 per 6 months compared to 167,282 for EHL (45% higher) [32]. Both studies used administrative claims data and information about severity of hemophilia, prescribed dosing, or administration dates and quantities administered are scarce or lacking. However, claims data can precisely quantify timing, quantities, and costs of products dispensed [32].

Nonetheless, when combining prescription dataset with medical records data, and applying exclusion criteria (e.g. active or prior inhibitor history) findings may differ completely. A recent study using the ATHNdataset, a US database of 138 American Thrombosis and Hemostasis Network affiliated HTCs found that as aggregate the median reduction of annual IU/kg for prophylaxis was 17% for EHL FVIII compared to prior SH abase case report fo rms showed that the ior factor treatmer ncy was lower (p ere patients on proph enced the discrepa hen using adm treatment, there a inhibitor treatmer

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Preliminary results of a study evaluating real-world outcomes with SHL and EHL in the US and several European countries (Spain included) found numerical differences in the mean total dose per week [34]. This study included 501 HA patients but only 66 patients were under EHL rFVIII treatment, and interestingly there were more moderate patients (59%) than severe patients. Regarding mean weekly dose, it was reported 106.2 and 101.29 IU/kg for SHL vs. EHL group, respectively, in the US, and in Europe, 102.8 and 71.5 (IU/kg), respectively [34]. This could suggest that the total per patient dose of FVIII product may differ between Spain and the United States.

At this point we must bring attention to one of the key assumptions we made when performing this study: the doses of SHL and EHL observed in the study by Chhabra et al. [6] were dispensed following strict clinical criteria and not others, such as economic ones. With this premise, we assumed that the prescribed doses of SHL and EHL met criteria of effectiveness that could be extrapolated to other clinical settings in other countries. The doses of rFVIII products dispensed to patients in the United States were obtained from real-world data and may be attributable to the effectiveness results in clinical practice, in which case they could be extrapolated to Spanish patients. However, further analysis is required on the consumption of rFVIII products in a greater number of patients and across different countries, including Spain.

It should be also considered that usually the scientific community accept clinical trial results f g to the Europea the applicab d be mainly medical population studied. lly carried out with t according to very s ne US and Euro be accepted in the s recomm

As ment e no Spanish data ava ed. A single-center re e was still limited a study [35],

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collected, but data on EHL products were not included, which is why those data could not be used in this study. According to this study, in a sample of 142 patients, the weekly dose of rFVIII per patient would be 5,806 IUs. The quarterly extrapolated dose would be 69,672 IUs, similar to the average quarterly doses per patient of SHL, which was 75,255 IUs in the Optum US database and 60,198 IUs in Truven US database ( Table 1).

In an Italian study published in 2017, the prescribed IUs of the different rFVIII products analyzed were estimated based on the summaries of product characteristics and not from the data of real-world patients with hemophilia A [39]. Another Italian cost-effectiveness study concluded that, compared with SHL products, the EHL efmoroctocog alfa would produce savings and an increase in quality-adjusted life years (QALY) [40]. This study assumed differences in effectiveness and consumption of rFVIII products based on a meta-analysis of data after switching from SHL to EHL products, but the method for this meta-analysis is still unpublished. However, a recent systematic review of the literature [41] did not support the potentially lower consumption of EHL compared with SHL products for all patients.

Several studies on the use of rFVIII products in real-world clinical practice have been published, but none provides specific or sufficient data on the IUs of SHL and EHL rFVIII products prescribed [42,43].

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limitations such as miscoding and patients changing insurance companies, and most importantly, they provide data of medicine dispensation, but there is no confirmation that these were actually administered.

There are also differences in pricing between US and Spain, as well as source of financing. In Spain, the reference price per IU of rFVIII is the same (€0.59) regardless of SHL or EHL rFVIII products and they are publicly financed by the National Health System. However, in the US the price of SHL and EHL is different and is mainly financed by private insurances. This factor could have conditioned the results obtained in the observational study by Chhabra et al. [6]. It must be noticed also that no other costs were analyzed, such as bleeding episodes, since it was limited to analyzing the acquisition costs of rFVIII obtained from the two databases described in the study [6]. Finally, Chhabra et al. [6] included a switch analysis of 29 patients, and the higher consumption evolution of EHL of these patients is persistent in the 1 year-period observed, providing further robustness of the higher consumption described for the population analysis that we used for our model.

## 5. Conclusions

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- In a real-world study conducted in the United States, the median IUs of rFVIII products dispensed were between 10% and 45% greater for extended half-life (EHL) FVIII products compared with standard half-life (SHL) rFVIII.
- In Spain, assuming the lowest number of IUs of SHL dispensed compared with EHL products, an average annual savings per patient treated with an SHL product of €11,227 would be generated, with a savings probability of 75.5% (i.e., the savings would be seen in 755 patients out of a cohort of 1,000).

## Authors' contributions

All authors contributed to the study design, the interpretation of the data, and the critical review of the publication, and approved the final version of the manuscript for publication. Carlos Rubio Terrés and Darío Rubio Rodríguez collected the data and developed the economic model.

## Declaration of interest

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# Additional information

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