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

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ABSTRACT

Background

In a real-world analysis (RWA) conducted in the United States (US), median international units (IUs) of extended half-life (EHL) recombinant coagulation factor VIII (rFVIII) dispensed were 10% to 45% greater than standard half-life (SHL) rFVIII. The mean IUs of each rFVIII dispensed quarterly were obtained from two databases (N = 776).

Methods

A probabilistic model in a 1-year time horizon was used in order to analyze the cost

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

1. Introduction

Hemophilia A (HA) is a congenital hemorrhagic disease linked to an anomaly in the X chromosome, which leads to a deficiency in blood coagulation factor VIII (FVIII) [1]. It is more common than hemophilia B, accounting for 80% to 85% of all hemophilia cases [1], with an incidence of 1 case in every 5,000 males born annually [2].

Bleeding severity in hemophilia is generally correlated with the patient's level of coagulation factor [3]. Most bleeding events occur in the joints or muscles, especially in patients with the severe form of the disease. Some bleeding events may be life-threatening (intracranial, neck/throat, gastrointestinal) and require immediate treatment [4]. Standard treatment for HA is intravenous administration of FVIII, which may be plasma-derived or recombinant (rFVIII), given as prophylaxis or on-demand (episodic, as needed). Prophylaxis with FVIII replacement therapy (exogenous) to

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 price, EHL rFVIII would theoretically be more efficient than SHL rFVIII.

To the best of our knowledge, at the time of performing this analysis, Spanish data on the use of EHL rFVIII in real-world setting were still very scarce or key IUs data was lacking [22] in order to investigate the cost implication of these products, due to the relatively short experience with these products.

Recently, Chhabra et al. [6] conducted a real-world analysis (RWA) using de-identified data to analyze the IUs dispensed and expenditures related to SHL and EHL rFVIII products for patients with HA. It was a retrospective study that used two specialty pharmacy claims databases in the United States (the Optum Clinformatics Data Mart [Optum; Eden Prairie, MN] and the Truven Health MarketScan Research Dababases [Truven Health Analytics; Ann Arbor, MI]) and included 776 patients with HA (Table 1). The IUs of SHL and EHL rFVIII dispensed quarterly were analyzed via a cross-sectional study over a period of more than 2 years (Optum, from August 2014 to December

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. Design and methods

An economic cost analysis was conducted from the perspective of the Spanish National Health System, using a probabilistic model based on a second-order Monte Carlo simulation [23,24]. This type of model, the methodology for which has already been described [25–28], enabled us to do the following: (1) takes into account variability of patient characteristics and the uncertainty of the model's variables in a hypothetical cohort of 1,000 patients with the characteristics of the HA patients included in the study by Chhabra et al. [6], treated with SHL or EHL rFVIII products, and (2) calculate the probability of possible savings in patients treated with SHL rFVIII compared with EHL rFVIII products [24].

The probabilistic analysis was conducted, with the consideration that the IUs dispensed would be adjusted for gamma distributions and that the frequency of use of the different rFVIII for beta distributions [23].

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 Reference Price Order [21].

The cost of intravenous infusions was not considered in the analysis because, in accordance with Spanish clinical practice, the majority of patients receive the medication at home via self-infusion. The costs are expressed in 2019 euros (€).

The following analyses were conducted: firstly, a base case, including all SHL and EHL rFVIII products and their frequency of use in Spain, with the parameters indicated in Tables 1 and 2; secondly, an initial sensitivity analysis similar to the previous one, but considering the frequency of use of SHL and EHL rFVIII products described in the RWA conducted in the US [6], detailed in Table 3; and thirdly, an additional sensitivity analysis for the data from the study by Chhabra et al. [6] regarding patients initially treated with an SHL product who switched to an EHL product (Table 1).

3. Results

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 would increase to €16,350, with a savings probability of 79.9% (Table 4).

3.3. Sensitivity analysis 2: comparing the cost before (pre) and after (post) switching from SHL to EHL

Not switching treatment from a SHL rFVIII to an EHL rFVIII product would result in a greater annual mean savings per patient of €53,078, with a 99.9% savings probability (Table 4).

4. Discussion

Extended half-life products are being introduced gradually and progressively in the clinical practice worldwide [30,31]. However, real-life data on the use of these products and their impact on cost and routine management of hemophilia patients are still limited.

According to our probabilistic model, the use of SHL rFVIII products rather than EHL

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 SHL FVIII [31]. Another real-world study using specialty pharmacy database case report forms together with medical records, and standard data collection forms showed that the mean weekly dose of EHL rFVIII was not significantly different to prior factor treatment (107,8 vs. 101,0, respectively), although the mean dosing frequency was lower ($p < 0.001$) [33]. These two studies included a high proportion of severe patients on prophylaxis regimen (82.6% and 89% respectively) that could have influenced the discrepancies with our finding and the first two abovementioned studies. When using administrative claims databases without sufficient data on the disease and treatment, there are no information on treatment regimen or severity of the disease or inhibitor treatment that allow understanding of the higher dispensation observed.

Pivotal clinical trials of EHL for hemophilia A usually report results on the efficacy and safety of severe patients under prophylaxis treatment. Nonetheless, when reviewing the limited publications on the real-life experience with EHL rFVIII we observe an evolving trend of use of FVIII clotting factors also in non-severe population, especially in moderate patients [34,35].

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 from different countries to be applicable in foreign setting. According to the European Medicines Agency, there may be extrinsic factors that determine the applicability of foreign data to an European setting [36]. These factors would be mainly medical practice (i.e. prophylaxis ….), the definition of the disease, and the population studied. Regarding the doses, the calculation of the required ones is generally carried out with the same formula and the management of the patient is carried out according to very similar recommendations [1]. Possible ethnic differences between the US and Europe are not usually an impediment for the results of US clinical trials to be accepted in the European Union, but prospective analysis of potential ethnic factors is recommended [37].

As mentioned previously, at the time of performing this analysis, there were no Spanish data available on the number of IUs of SHL and EHL rFVIII products dispensed. A single-center results on the use of rFVIIIFc were presented recently, but the sample was still limited and lacked specific data to be used in this study [38]. In a previous study [35],

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].

It should be noted that the lower number of IUs of SHL rFVIII products dispensed compared with EHL rFVIII products reported for patients with hemophilia A in the United States was consistent with what was found in an analysis of 296 patients with hemophilia B from the Truven database treated with an SHL recombinant factor IX product compared with those treated with an EHL product [44].

This study was not without limitations. The real-world study from which the present economic study is derived is a retrospective study using claims data with a limited predictive power of its results [6]. The IUs of rFVIII products dispensed quarterly were obtained from two databases for patients in the United States [6], not from Spanish patients. However, as detailed elsewhere, the Optum database and Truven database altogether contain the pharmaceutical and medical data of approximately 166.5 million individuals from across the US, including patients with hemophilia and could provide a representative number of patients; thus, they could be extrapolated to HA patients

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

In summary, our study demonstrates that an annual savings per HA patient treated with SHL compared with EHL products of €11,227 can be obtained in the base case, with a savings probability of 75.5%. The maximum savings (€53,078 per patient) would be achieved if treatment was not switched from an SHL to an EHL product. Considering the frequency of IUs dispensed in the US real-world analysis by Chhabra et al. [6], and not the frequency in the Spanish population, the savings probability would be 79.9%. The probabilistic model found higher expenditures over one year for hemophilia A patients using EHL versus SHL products. The use of SHL instead of EHL would amount to cost savings to the National Health System in Spain. The findings of this analysis could be considered alongside a thorough clinical evaluation when determining an optimal therapeutic strategy.

Article highlights

- 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

CRT and DRR are employees of Health Value, who were paid consultants to Pfizer in connection with the conduct of this study and development of the manuscript. CP and HKK work at Pfizer SLU. Pfizer is the manufacturer of Refacto AF, a product mentioned in this article. Manuscript formatting support was provided by Terry ONeill at Peloton Advantage, LLC, an OPEN Health company, and funded by Pfizer; no contribution was made to editorial content. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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