PK-driven prophylaxis versus standard prophylaxis: when a tailored treatment may be a real and achievable cost-saving approach in children with severe hemophilia A

Pasca Samantha, Milan Marta, Sarolo Lucia, Zanon Ezio

Hemophilia Center, University Hospital of Padua

Abstract

Background: Prophylaxis is the gold standard for the treatment of children with severe hemophilia. In the last years a new approach to prophylaxis based on annual bleeding rate (ABR), pharmacokinetics (PK) and lifestyle of each patient has begun to be adopted in hemophilia treatment.

Aim: Aim of our observational retrospective study was to evaluate whether in a group of children with severe hemophilia A (HA) a tailored approach may be used to replace standard therapy, reducing costs.

Methods: PK evaluation was carried out in six hemophiliac children followed at our Hemophilia Center, and already receiving recombinant factor VIII (rFVIII) on prophylaxis, using a computing program (*MyPKfit*®). Bayesian curve was created for each child and tailored prophylaxis was estimated considering a trough level of 1%.

Results: The weekly frequency of infusions was reduced in one patient, while it was slightly increased in three children. As to the remaining children, only the dosage was changed. Scheduled follow-up revealed a complete adherence to treatment, a reduction of bleeds using PK-regimen and a general improvement in the quality of life. The comparison between the direct and indirect costs of treatment during standard and PK-driven prophylaxis showed a total saving of € 54,797.40 (-10.67%) in case of tailored prophylaxis

Conclusion: A therapeutic approach based on PK and clinical characteristics of each patient may change standard treatment. Based on our results, tailored prophylaxis could be an effective option for children with HA reducing costs.

Key words

Hemophilia treatment, replacement therapy, cost of treatment, quality of life

Background

Hemophilia A is a rare X-linked disorder characterized by a partial or total deficiency of coagulation factor VIII (FVIII) that leads to frequent hemarthroses, urogenital or gastrointestinal bleeding, intracranial hemorrhage or large hematomas [1,2]. The age of hemophilia diagnosis depends on the level of baseline FVIII. In case of severe hemophilia (FVIII <1%), diagnosis usually occurs at an early age as a result of unexplained bleeding or when the baby starts to crawl and manifest the first hematomas.

In order to reduce the risk of bleeding and prevent the onset of a debilitating and deforming arthropathy following continuous hemarthroses, these patients are treated on prophylaxis with FVIII concentrates [3]. Primary prophylaxis, started early at a dosage of 25-40 IU/kg, is the gold standard of treatment [4,5].

The study of pharmacokinetics (PK) began several years ago when the first coagulation factor concentrates were marketed [6]. PK is necessary to know the plasmatic FVIII reached after treatment and its circulating permanence is needed to guarantee acceptable hemostasis. Plasma levels of replacement factors are influenced by the patient's age, weight and metabolic characteristics, which determine the different PK among patients [7,8]. Classic measurement of PK follows the International Society on Thrombosis and Haemostasis (ISTH) guidelines. Patients are infused with 50 IU/ kg of FVIII after a wash-out of 72 hours, and plasma samples are then collected at 0, 30 ', 60', 3h, 6h, 12h, 24h, 48h. Thus the data obtained are used to create a PK-curve, different for each patient. In children the seven classic spots can be reduced to five, but it remains difficult to conduct a PK-survey of all hemophiliac subjects [9].

Today, the development of statistical methods based on a smaller number of samples in a shorter time permits to study PK-profiles in an increased number of patients [10]. The success of prophylaxis in hemophilia patients depends on the maintenance of an appropriate trough level 1% in case of subjects with severe hemophilia. Other important PK data that must be evaluated are the area under the curve (AUC), the maximum peak of the FVIII level obtained after infusions, the clearance, and the half-life of FVIII [11].

The tailored approach to hemophilia treatment is based on the uniqueness of each patient. Everyone has different pharmacokinetic properties, does more or less intense physical activity, has a marked hemorrhagic phenotype or has a hemophiliac arthropathy, etc. In developed countries, where access to treatment is basically guaranteed, the primary goal of tailored therapy is to reach “zero” in the annual bleeding rate (ABR), and make QoL of hemophiliac patients comparable to that of healthy subjects. Even though in a patient suffering from hemophilia prophylaxis is particularly expensive, less frequent bleeding episodes, associated with improved management of the dosage and the number of infusions derived from PK assessment, may lead to a significant reduction of costs.In

developing countries, where only limited resources are available and access to clotting factor concentrates is often restricted to a small number of patients, a tailored therapy could allow an optimal use of these drugs; it will also ensure treatment to an increasing number of subjects, of course always trying to achieve the "zero ABR" objective. Less bleeding, fewer hemarthroses, a decreased rate of hospitalization, a lower need for instrumental and laboratory examinations, and reduced use of clotting factor concentrates or by-passing agents, may improve individual patient's QoL, reduce costs, and increase the available resources [12,13].

Aim

The aim of our observational retrospective study was to evaluate whether in a group of children with severe HA a tailored PK-driven approach may be used to replace the standard therapy, reducing costs.

Patients and Methods

- *Study design*

This is an observational retrospective study on children with severe hemophilia A, already on prophylaxis with rFVIII (Advate® –Baxalta Shire) and followed at the Hemophilia Center of Padua (Italy).

The study was divided into two different phases, and subsequently compared:

1) PK-driven phase: for each child, we evaluated the costs of PK-driven prophylaxis with Advate®, the costs of further treatments with Advate®, and the indirect costs in case of bleeding, from PK-assessment to 31 December 2016.
2) Standard phase: for each child, we evaluated the costs of standard prophylaxis with Advate®, the costs of further treatments with Advate®, and the indirect costs in case of bleeding for an equal period of time, but before PK-assessment.

- *Patients*

Inclusion criteria: all pediatric patients <12 year-olds with severe hemophilia A, and already treated on prophylaxis with Advate®. No presence of FVIII inhibitors. Informed consent to study was signed by parents.

Exclusion criteria: all patients>12 year-olds. Patients with mild or moderate hemophilia A. Patients treated with other FVIII concentrates than Advate®. Patients treated only on demand with FVIII concentrates. Presence of FVIII inhibitors. Parents refused to sign informed consent.

- *Protocol*

This an observational retrospective study, its nature did not interfere with the common protocol of treatment applied at our Center. All data were analyzed after 31 December 2016.

Data source: All the information about the hemophiliac patients treated at our Hemophilia Center is recorded on their personal folders. All data evaluated in this study were previously recorded on these folders.

Visits: Following the usual protocol applied at our Hemophilia Center when a new prophylaxis is started, we have planned these checks: telephone contacts at 1 and 3 months to assess adherence to therapy, and scheduled visit to the Hemophilia Center at 6 months. Supplementary visits are provided only in case of hemorrhagic events or changes in the treatment. During the visit at our Hemophilia Center we asked all patients four short questions concerning their quality of life (QoL): 1) Is this new prophylaxis easy to follow? 2) On your opinion, has your QoL improved or not? 3) Why has your QoL improved? 4) Would you to go back to previous treatment? All responses were recorded, but not statistically evaluated.

- *Prophylaxis regimens*

Standard prophylaxis: All patients were already treated with Advate® three times a week.

PK-driven prophylaxis: To determine the PK profile and subsequent tailored prophylaxis, each child was infused with Advate®50 IU/kg, and plasma samples were then collected at: T0 (baseline); T1 (20' after infusion); T2 (4 hrs after infusion).

Real prophylaxis was carried out basing on theoretical dose of concentrate to infuse to each patient.

- *Pharmacokinetics*

Pharmacokinetics was assessed by the web-based device *MyPKfit*® (Baxalta-Shire) using the Bayesian model to estimate PK-curve and tailored prophylaxis for each child.

Calculated pharmacokinetic data were: 1) FVIII Clearance (dl/hr/kg); 2) Steady state volume (dl/kg); 3) FVIII half life (hrs); 4) Time to reach +1% from baseline FVIII (hrs); 5) Trough level. 72 hours wash-out before PK evaluation was not required with this device.

- *Economic evaluation*

Cost of annual prophylaxis: An economic evaluation was performed comparing standard and PK-driven prophylaxis (each child/per year) considering the unit cost of Advate® approved in our Region (€ 0.65/IU).

The costs of PK-driven prophylaxis are assessed considering available vials of Advate® (250 IU, 500 IU, 1000 IU and 2000 IU), and the real infused doses to each patient.

Cost of bleeding: The costs of all further treatments with Advate®, due to bleeding, during standard and PK-driven phases were assessed and added to prophylaxis costs for the final economic evaluations.

Indirect cost of bleeding: The costs of instrumental and standard laboratory examinations along with specialist visits based on the rates established by our Region (*Tariffario Prestazioni Specialistiche Ambulatoriali della Regione Veneto-Specialist Outpatient Service Rates of the Veneto Region*) were also considered. Standard laboratory examinations: inhibitors of FVIII (€ 12.60), FVIII:C (€ 15.80), aPTT (€ 2.80), PT (€ 2.85), and blood count (€ 5.15). Instrumental examination: magnetic resonance imaging (€ 284.90), muscle ultrasound (€ 31.30), and articular ultrasound (€ 45.60). Specialist visits: Hemophilia Center visit (€ 20.50), orthopedic visit (€ 20.50) and physiatric visit (€ 20.50). No indirect costs due to days of work lost by parents and to home-hospital transfer costs were included because of the difficulty of in standardizing them.

- *Statistical analysis*

Due to the observational nature of this study no particular statistical strategy was adopted. The tables of statistical analysis were produced with the Statistical Analysis System (SAS) release n. 9.2 in Windows 7 professional environment

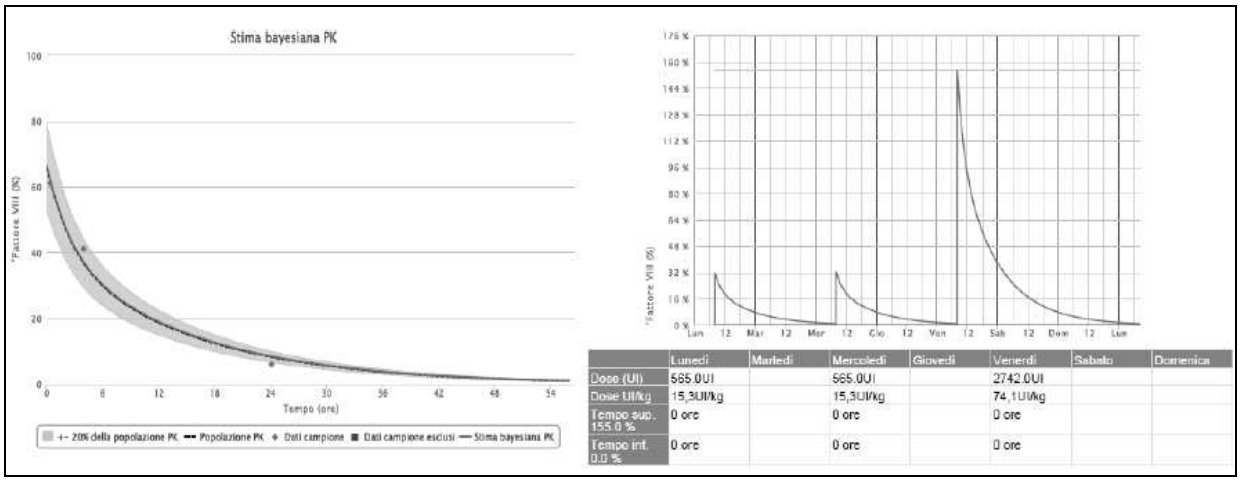
All the variables collected were summarized in the tables. The economic evaluation between standard and PK-driven phases were expressed as €/year. The difference between the two treatment were reported as (€/year) and as percent (%).

Comparative statistics between standard and PK-driven prophylaxis were performed with the Mann-Whitney Test ($p<0.05$).

Results

Six children (2-9 years) with hemophilia A, already treated with recombinant FVIII, octocog alfa (Advate®), and followed at our Hemophilia Center, were included in this study.

Bayesian curve and following tailored prophylaxis for each child were assessed with *MyPFfit*® device, estimating a trough level of 1% (Fig. 1)



	Lunedì	Martedì	Mercoledì	Giovedì	Venerdì	Sabato	Domenica
Dose (UI)	565.0 UI		565.0 UI		2742.0 UI		
Dose UI/kg	15,3UI/kg		15,3UI/kg		74,1UI/kg		
Tempo sup. 155.0 %	0 ore		0 ore		0 ore		
Tempo int. 0.0 %	0 ore		0 ore		0 ore		

Fig.1 Example of Bayesian curve and tailored prophylaxis calculated by *MyPKfit*® device (PD-03)

The difference between the previous standard prophylaxis regimen for each child and the tailored PK-driven prophylaxis estimated by *MyPKfit*® device are summarized in Table 1. Given the availability of 250 IU, 500 IU, 1000 IU and 2000 IU vials, we have divided the dosages into "theoretical", obtained by *MyPKfit*® device and "real". Economic evaluation has been performed considering the real infused dosages.

Patient ID	Weight (Kg)	Dose (IU/kg)	Infusion dose (IU)	Frequency of prophylaxis	Infusions (no/yr)	Dose (IU/kg)	Theoretical dose to infuse (IU)	*Real infused dose (IU)	Frequency of prophylaxis	Infusions (no/yr)
PD-02	28	35.7	1000	3 times/wk	156	37.2	1042	alternate 1000 and 1250	every 72 hr	110
PD-03	37	27.0 54.0	1000 2000	2 times/wk + 1 time/wk	156	15.3 74.1	566 2740	500 2750	2 times/wk + 1 time/wk	156
PD-04	11	43.5	500	3 times/wk	156	29.7	327	alternate 250 and 500	every other day	182
PD-05	29	34.5	1000	3 times/wk	156	14.6 69.7	423 2021	500 2000	2 times/wk + 1 time/wk	156
PD-06	22	22.7	500	3 times/wk	156	20.3	447	500	every other day	182
PD-08	20	25.0	500	3 times/wk	156	21.1	422	alternate 250 and 500	every other day	182

Table 1 Difference between standard (white) and tailored (grey) prophylaxis estimated by *MyPKfit*® device. * Real infused dose considering the PK profile for each child and the available vials (250 IU, 500 IU, 1000 IU, and 2000 IU).

PK-driven prophylaxis showed that three children needed an increase in infusions to maintain a through level ≥1% over the week, reducing hemorrhagic risk, and improving physical activity. Two children only needed a change in dosage, without any modification to frequency. The remaining child decreased annual infusions (-46/year), with a consequent reduction of annual consumption of rFVIII (-20,250 IU/year).

Follow-up at 1and 3 months, performed by telephone contact, revealed good adherence to therapy, without bleeds or changes in the treatment. The same results were achieved at 6 months and were reported during the scheduled visit to the Hemophilia Center. Seven bleeds occurred in our six patients during standard prophylaxis, one of which was a hemarthrosis (PD-03). Instead, only two minor bleeding episodes occurred in the patients treated with tailored PK-driven prophylaxis, and one of them was a mild traumatic event (PD-04). All bleeds needed additional treatments with FVIII concentrate (on-demand treatments). Economic evaluation was subsequently performed comparing standard and PK-driven phases. The results are reported in Table 2.

Patient ID	Cost SP (€/yr)	No. bleeds SP	*IU on-demand	Cost on-demand (€/yr)	Total cost SP (€/yr)	Cost PK-P (€/yr)	No. bleeds PK-P	*IU on-demand	Cost on-demand (€/yr)	Total cost PK-P (€/yr)	Δ (€/yr)	Δ (%)
PD-02	101,400	1	*1000*	650	102,050	80,438				80,438	-21,612	-21.18
PD-03	135,200	4	*31000*	20,150	155,350	126,750	1	*2000*	1,300	128,050	-27,300	-17.57
PD-04	50,700				50,700	46,800	1	*2000*	1,300	48,100	-2,600	-5.13
PD-05	101,400	1	*1500*	975	102,375	101,400				101,400	-975	-0.95
PD-06	50,700	1	*1000*	650	51,350	50,700				59,150	8,450	16.67
PD-08	50,700				50,700	49,920				44,362	-6,338	-12.50
TOTAL	**490,100**	**7**	***34500***	**22,425**	**512,525**	**456,008**	**2**	***4000***	**2,600**	**458,608**	**-53,917**	**-10.52**

Table 2 Economic comparison between total costs of rFVIII during standard phase (SP) and PK-driven phase (PK-P). Unit cost of Advate®: € 0.65 /IU. In grey the difference (Δ) between total costs of standard phase and PK-driven phase expressed in €/yr and %. *IU: international unit.

PK-driven prophylaxis was assessed as cost-saving in 5/6 cases (83.4%). The total saving was of € 53,917/year for all six patients, with a mean of € 8,986/year per child. Among these, the total saving due to the changes made to prophylaxis regimen was of € 34,092/year, while the remaining saving of € 19,825/year was associated with a reduction of the on-demand rFVIII consumption during PK-driven prophylaxis..

The additional costs of each bleeding are reported in Table 3. During the standard phase, at least one visit to Hemophilia Center was made by patients PD-02, PD-05, and PD-06. Due to hemarthrosis, the patient PD-03 visited our Hemophilia Center four times, until resolution. The latter child needed only one visit during each of the other minor bleeds. In order to assess the severity of hemarthrosis, the patient PD-03 underwent articular and muscle ultrasound, followed by a magnetic resonance imaging (MRI), and by an orthopedic visit and a physiatric one. Standard laboratory examination (PT, aPTT, FVIII:C, FVIII-inhibitors, and blood count) were performed for each bleeding events. The total indirect costs during the standard phase amount to € 999.80. During the PK-driven phase, patients PD-03 and PD-04 visited the Hemophilia Center once. In this case,

standard laboratory examination (PT, aPTT, FVIII:C, FVIII-inhibitors, and blood count) were carried out for each bleeding events as well. The total indirect costs during the PK-driven phase are of € 119.40. The difference between the total costs of standard and PK-driven prophylaxis showed a saving of € 54,797.40 (-10.67%) in the case of the tailored treatment. A comparison of the total costs incurred in the two phases through the Mann-Whitney test ($p<0.05$) did not reveal a statistically significant difference ($p=0.57$).

Patient ID	*Direct costs SP (€/yr)	°Indirect costs SP (€/yr)	Total cost SP (€/yr)	*Direct costs PK-P ((€/yr)	°Indirect costs PK-P (€/yr)	Total cost PK-P (€/yr)	Δ (€/year)	Δ (%)
PD-02	102,050.0	59.7	102,109.7	80,438.0		80,438.0	-21,761.7	-21.31
PD-03	155,350.0	820.7	156,170.7	128,050.0	59.7	128,109.7	-28,061.0	-17.96
PD-04	50,700.0		50,700.0	48,100.0	59.7	48,159.7	-2,540.3	-5.01
PD-05	102,375.0	59.7	102,434.7	101,400.0		101,400.0	-1,034.7	-1.01
PD-06	51,350.0	59.7	51,409.7	59,150.0		59,150.0	7,740.3	15.05
PD-08	50,700.0		50,700.0	44,362.0		44,362.0	-6,338.0	-12.50
TOTAL	**512,525.0**	**999.8**	**513,524.8**	**458,608.0**	**119.4**	**458,727.4**	**-54,797.4**	**-10.67**

Table 3 Economic comparison between total costs (direct and indirect) of standard phase (SP) and PK-driven phase (PK-P). *Direct costs: total cost of treatment with Advate (prophylaxis and on-demand) during the different phases. °Indirect costs: standard laboratory examinations, instrumental examinations, and specialist visits.

The four short oral questions administered to the children during the scheduled visit to our Hemophilia Center revealed a general improvement in QoL given the fewer bleeding episodes. Three patients also associated their QoL improvement with the possibility on performing more physical activity. For one patient, the reduction of infusion frequency was the most important goal achieved thanks to the new regimen. None of the patients wanted to go back to the previous treatment.

Discussion

The aim of our observational retrospective study was to evaluate whether in a group of children with severe HA a tailored PK-driven approach, cropped on the patient, his characteristics and needs, may be used to replace the standard therapy, reducing costs.

During acute bleeding episodes or in case of hospitalization, the child is compelled to remain at home and therefore to lose school days, while his parents are often forced to take time off work. Prophylactic treatment in hemophilia is usually very expensive, particularly for the high cost of the drug used, which rises greatly in case of bleeding. More attention to the treatment regimen adopted for each patient is therefore necessary to deal with these problems.

In recent years, different analyses have been performed to evaluate the cost-effectiveness or the cost-utility of these therapies [14,15]. Utility generally refers to the value that the general population attributes to the different states of health; the values are expressed on a numerical scale ranging from 0 (death) to 5 (perfect health). Sometimes, results may even be less than zero when the outcome of the intervention is perceived by the patient as worse than death itself [15].

A recent review by Valente et al [16] considered six cost-effectiveness and cost-utility studies [14,15,17-22] of patients with hemophilia A, comparing on-demand treatment with clotting factor concentrates to prophylaxis.

Prophylaxis showed excellent outcomes improving the overall QoL, reducing bleeds alongside the risk of developing a severe hemophiliac arthropathy compared to on-demand treatment, though with a significant increase in FVIII consumption and costs. However, in these studies indirect costs such as days of school/work lost, and costs of transfer from home to the hemophilia center, or other indirect costs not related to clotting factor consumption, such as laboratory and instrumental examinations that are often required in case of acute bleeding, were not taken into consideration.

It is therefore essential to identify a therapeutic regimen that can improve treatment compliance and effectiveness. The degree of severity of hemophilia, genotype of each patient, lifestyle and PK-profile can help clinicians to determine the different treatments [11,21].

Iannazzo et al [24] compared standard prophylaxis to PK-driven prophylaxis in patients with severe hemophilia A in terms of cost-effectiveness. The study was conducted using the web-based device, *MyPKfit*®, as done in our work. A drug-economic model was created to assess the two different approaches in a simulated cohort of 10000 hemophiliacs. Performed simulation produced the following results: 1. 10.6% of patients treated on standard prophylaxis (30 IU/kg every other day) maintained a trough level <1%, while 27.8% of them could keep a plasmatic FVIII> 5%; 2. Instead, the same patients treated with tailored and PK-driven prophylaxis all had a trough level between 1-5%. A higher level of circulating FVIII is also associated with a reduction in bleeds that requires an increase in the consumption of concentrate, resulting in higher costs. The costs of prophylaxis should be considered together with the costs to be paid to prevent hemorrhage so as to assess effectiveness and sustainability of hemophilia treatment in the correct way. Using *MyPKfit*® device, Iannazzo et al [22] estimated that a tailored approach to hemophilia was preferable to the standard one, because it reduced ABR, improved QoL, and reduced costs. PK-assessment for each patient allowed to simulate a change from standard prophylaxis (30 IU/kg) to variable prophylaxis (10-100 IU/kg) based on individual characteristics. Intensity of treatment was reduced in patients with favorable PK data (high half-life and trough level), and was increased in patients with less favorable

PK-parameters. The PK-driven simulation led to a theoretical saving of € 5,000 patient/year, and € 30,000/year thanks to the bleeding episodes avoided.

In our study, all economic evaluations have been performed considering the real infused dosages of rFVIII during the PK-driven treatment. Two children on PK-guided prophylaxis only needed a light change of dosage, without any modification of treatment and keeping three infusions a week. In these two young patients, in order to maintain a sufficient level to ensure a good hemostasis also over the weekend, the infused dose was increased. Three children needed to increase infusion frequency, from three times/week to every other day, to maintain a through level ≥1% over the week, reducing hemorrhagic risk, and improving physical activity. The remaining child improved his QoL decreasing annual infusions (-46/year), with a reduction in annual consumption of rFVIII (-20,250 IU/year). As reported by Iannazzo et al [22], a tailored approach to hemophilia treatment is likely to reduce the costs in our case as well. PK-driven prophylaxis proved to be cost-saving for 5/6 patients (83.4%). The amount saved accounted for € 53,917/year, with a mean of € 8,986 patient/year; of this, a saving of € 19,825/year depended on the lower consumption of on-demand units of rFVIII. The costs related to clotting factor concentrate consumption are the major costs in hemophilia patients, but in our study indirect costs due to bleeds, such as standard laboratory examinations, instrumental examinations and/or specialist visits needed, were also evaluated. During PK-driven prophylaxis indirect costs decreased. The total costs, including direct and indirect costs, were reduced by 10.67% during tailored prophylaxis. Six months after the beginning of PK-driven prophylaxis, all patients showed a general improvement in QoL due to reduced bleeding, in some cases associated with either, the possibility of performing more physical activity or less frequent infusions.

PK-driven prophylaxis was proved to be an effective approach to treating hemophiliac patients as stated by Santoro et al [23] or by Lissitchkov et al [24]. In this work the authors have proved that a PK-driven prophylaxis with human-cl rhFVIII provided bleeding protection and reduced the frequency of infusions to twice weekly or less in many patients. However, since prophylaxis based on clinical features of patients is commonly applied worldwide, PK-driven prophylaxis is more rarely used due to the difficulty in performing this type of analysis in the absence of such devices as *MyPKfit*® or equipped laboratories. A study on the use of the *MyPKfit*® device, has recently been published by Álvarez-Román et al [25]. The authors show the importance of this tool to evaluate the PK in 27 patients with severehemophilia A, already treated with Advate®, and to establish a tailored prophylaxis for each of them based on their clinical and pharmacokinetic characteristics, and on their daily needs. The authors found this device particularly useful in patient education due to an

attractive and informative output graph that helped improve adherence to treatment. However no pharmacoeconomic evaluations were performed in this study.

Classic measurement of PK follows the ISTH guidelines [9], but it is very difficult to perform this assessment due to the high number of plasma samples required. It is therefore desirable that in the near future the research groups [10] who are committed to the creation of simplified algorithms for PK determination may succeed in completing their work, providing clinicians with this valuable therapeutic tool. The Web-Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo) is an example of useful web-based service that can to help clinicians to perform more PK assessments before starting a new prophylaxis with coagulation factors concentrates. WAPPS-Hemo investigators have developed prototypal population pharmacokinetics models for several FVIII and FIX concentrates, using PK studies sourced from pharmaceutical companies and independent hemophilia centers. A multi-compartmental model has been created using a mixed-model approach for derivation and Bayesian forecasting for estimation of individual data. The WAPPS-Hemo could to be made easier to perform PK assessments reducing the number of plasma samples by adopting these population PK approaches [10].

In the future, PK assessment will be increasingly important in order to better understand the PK profile of new extended half-life (EHL) drugs, and to use them in the best possible way. As reported by Iorio et al. [26], in case of hemophilia B treatment, the optimal sampling times need to be adapted to the new prolonged half-life products to better create their PK profile. This was also proposed by Zhang et al [27], who developed a population PK model based on FIX activity levels of 104 patients who had received treatment with recombinant FIX fusion protein (rFIX-FP). This new model seems to correlate with the clinical data observed, supporting a prolonged dosing of EHL-FIX with intervals of up to 2 weeks. To reduce the frequency of infusions and consequently to reduce the costs of treatment are the goals pursued by the new EHL products, but a standardized model to evaluate their PK is needed to correctly assess their efficacy and their suitability over the time.

One imitation of our study is the small sample size , but the hemophilia is a rare disease and only a part of patients followed at our Hemophilia Center are children. Among them a few patients were treated with other coagulation factors other than Advate®, sothey were excluded from this evaluation. Furthermore, it was impossible to carry out a pharmacokinetic analysis in some patients for lack of compliance due to their young age. Another limitation is the retrospective nature of this study. Some minor bleeding events may have escaped our attention as they were not reported by parents. Nonetheless the relatively short duration of observation has greatly reduced the likelihood of such bias. What is very important for these patients is the impact that this change in treatment

may have on their quality of life, and only a few oral questions are not sufficient to establish it. Undoubtedly a standardized written questionnaire could be a better choice

Conclusion

Our study is the first study that has evaluated the costs of PK-driven prophylaxis versus standard prophylaxis in children with hemophilia, and in real life, considering both direct and indirect costs of treatment. Pharmacokinetics is unique to each subject and can help clinicians optimize treatments improving the QoL, reducing infusions as well as bleeding. PK-driven prophylaxis can also decrease the costs of therapies, which are usually very high in hemophilia patients.

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