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Letter to the Editors-in-Chief

Savings without changing: How to use the *MyPKfit*® device to improve treatment strategies in a cohort of patients with haemophilia A

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ABSTRACT

Background: The real goal on haemophilia treatment is to combine efficacy, safety, improvement in quality of life and cost-savings. Sometimes the choice for reaching this result is to switch the patients to an extended half-life (EHL) drug. In case of haemophilia A this goal is not always achieved due to the less pharmacokinetic (PK) differences among EHL and standard concentrates. A better and regular use of available tools, as *MyPKfit*®, can then optimize the treatment without distorting therapy or changing concentrate.

Methods: We now report our experience with a population of severe or moderate haemophilia A patients treated with octocog-alfa (Advate® –Shire Takeda) and in which a tailored prophylaxis with *MyPKfit*® has been assessed.

Results: PK evaluations of 14 patients were carried out. A Bayesian curve and a tailored prophylaxis were assessed individually employing PK data. The weekly frequency of infusions was reduced in three severe patients, it was increased in four while it remained the same in the others five patients. The annual consumption of concentrate was reduced in 81.8% of patients. A subsequent economic evaluation carried out for each of the twelve severe haemophilia A patients included in this analysis, in which we have compared the standard and the PK-driven prophylaxis, showed that an optimized treatment can lead to an annual average saving of € 20,525 (−15.8%).

Conclusions: The use of *MyPKfit*® for a tailored prophylaxis may lead to a more rational use of available resources through an easy correction of the treatment strategies without distorting the individual patient therapy.

When we talk about the treatment strategies in patients with haemophilia the real goal is to combine efficacy and safety, as required by physicians; improvement of the quality of life (QoL), as required by patients; and cost-savings, as requested by the National Health System.

Sometimes the choice performed by the clinicians to reach this goal is to switch the patients to another concentrate, usually an extended half-life (EHL) which allows to reduce the number of infusions, and in some cases the amount of prescribed concentrate. If the switches to EHL products in haemophilia B patients leads to a real reduction of infusion frequency, with a consequent reduction of factor consumption, a reduction of costs and an evident improvement in the QoL for the treated patients; in cases of haemophilia A this is not always achieved due to the less pharmacokinetic (PK) differences, especially the half-life, among EHL and standard concentrate.

Until now, in Italy, only one EHL product has been marketed, efmoroctocog-alfa; its PK features have revealed a mean half-life of 19 h, while the other concentrates available to us present a mean half-life between 11.2 h (moroctocog-alfa) and 17.1 h (simoctocog-alfa) [1]. Efmoroctocog-alfa is usually prescribed at a dosage of 50 IU/Kg every 3–5 days, based on the A-Long Trials [2,3], but this regimen can be changed following the individual response to treatment. The other products are indeed administered at a dose of 25–40 IU/Kg three times a week or every other day, as reported by the Malmöe protocol [4].

The number of annual infusions then result less frequent in cases of patients treated with this EHL, while the amount of concentrate, and consequently the costs, are not always reduced due to the recommended dose increase compared to standard protocols. A better and regular use of available tools, that easily assess the PK profile of each patient and subsequently estimate the optimal prophylaxis with the standard products which can then optimize the treatment without changing the factor VIII concentrate.

We now report our experience with a population of severe or moderate haemophilia A patients treated with octocog-alfa (Advate® –Shire Takeda) and in which a tailored prophylaxis with *MyPKfit*® has been assessed to optimize their therapeutic regimen. All reported data were referred to one-year standard prophylaxis compared to one-year tailored prophylaxis for each switched patient.

The pharmacokinetic evaluations of 14 patients were carried out, nine of them were children (< 12 years). The patients on prophylaxis were 87.5%, while the remaining two patients previously treated on-demand presented an annual bleeding rate (ABR) > 5. Pharmacokinetics was assessed by the web-based device *MyPKfit*® (Shire-Takeda) using the Bayesian model to estimate the PK-curve and the tailored prophylaxis for each patient, based on a trough level chosen by the physicians. Calculated pharmacokinetic data were: 1) FVIII Clearance (dl/h/kg); 2) Steady state volume (dl/kg); 3) FVIII half life (hrs); 4) Time to reach +1% from baseline FVIII (hrs). The established trough level was 1% and 3% for patients with severe and moderate haemophilia respectively. Each patient was infused with Advate®50 IU/kg, and plasma samples were then collected at: T0 (baseline); T1 (20′ after infusion); T2 (4 h after infusion) to assess their PK profile and subsequently their tailored prophylaxis. Four patients (PD-02; PD-04; PD-06 and PD-08) were also considered in our previous study [5] on cost-effectiveness of PK-driven prophylaxis.

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Table 1
Previously prophylaxis and tailored approach (grey) for each patient. *Patients with moderate HA. OD: on demand treatment. Patients previously OD were excluded from comparison. °: annual bleeds of moderate patients were excluded from mean evaluation.

Patient ID	Age (years)	Half-life (hours)	Time >1% (hours)	Previously prophylaxis	No. of infusions/yr	IU/kg for prophylaxis /yr	Annual bleeds (no.)	New prophylaxis	No. of infusions/yr	IU/kg for prophylaxis/yr	Annual bleeds (no.)	Δ (%) (IU/kg)	Δ (%) (infusions)
***PD-01**	9	11.8	NA	50.0 IU/kg OD	NA	NA	8°	37.8 IU/kg every other day	183	6917	3°	NA	NA
PD-02	11	12.1	63.0	53.6 IU/kg 3 times/wk	156	8362	1	37.2 IU/kg every 72 h	122	4538	0	−45.7	−21.8
PD-03	9	10.5	56.0	36.0 IU/kg 3 times/wk	156	5616	4	34.9 IU/kg 3 times/wk	156	5444	1	−3.1	=
PD-04	2	8.9	53.0	43.5 IU/kg 3 times/wk	156	6786	0	29.7 IU/kg every other day	183	5435	1	−19.9	+17.3
PD-05	10	10.6	72.0	34.5 IU/kg 3 times/wk	156	5382	1	33.0 IU/kg 3 times/wk	156	5148	0	−4.4	=
PD-06	7	9.5	59.0	22.7 IU/kg 3 times/wk	156	3541	1	20.3 IU/kg every other day	183	3715	0	+4.9	+17.3
***PD-07**	11	12.9	NA	45.5 IU/kg OD	NA	NA	7°	51.9 IU/kg every 72 h	122	6332	2°	NA	NA
PD-08	7	11.6	63.0	25.0 IU/kg 3 times/wk	156	3900	0	21.1 IU/kg every other day	183	3861	0	−1.0	+17.3
***PD-09**	27	15.1	NA	32.2 IU/kg 3 times/wk	156	5023	2	30.4 IU/kg 3 times/wk	156	4742	2	−5.6	=
PD-10	38	14.9	84.0	33.4 IU/kg 2 times/wk	104	3474	6	19.3 IU/kg every 72 h	122	2355	4	−32.2	+17.3
PD-11	57	14.4	74.0	22.7 IU/kg 3 times/wk	156	3541	4	20.9 IU/kg every 72 h	122	2550	3	−28.0	−21.8
PD-12	21	12.3	66.0	27.3 IU/kg 3 times/wk	156	4259	2	25.9 IU/kg 3 times/wk	156	4040	1	−5.1	=
PD-13	8	11.6	63.0	25.0 IU/kg 2 times/wk	104	2600	0	26.1 IU/kg 2times/wk	104	2714	0	+4.4	=
PD-14	14	12.7	69.0	32.8 IU/kg 3 times/wk	156	5117	2	37.7 IU/kg 2times/wk	104	3921	0	−23.4	−33.3
Mean	**17.6**	**12.0**	**65.6**		**147**	**4800**	**1.9**		**145**	**4039**	**1.0**	**−15.8**	**−1.4**

We have decided to perform a pharmacokinetic evaluation in our patients treated with Advate®, especially those who used a greater quantity of concentrate to evaluate if it was possible to improve the treatment by reducing costs. Furthermore, some of these patients presented bleeding due to the fact that perhaps the standard treatment, 2–3 times a week, could not give them the necessary and sufficient hemostatic coverage. Another reason for assessing the PK was that many of the patients were children, and had changed their lifestyle and their metabolism with growth. Moreover, the availability of a device such as *MyPKfit*® made it possible to carry out the pharmacokinetic profile more easily.

The difference between the previous standard prophylaxis regimen for each patient and the tailored PK-driven prophylaxis assessed by *MyPKfit*® device was summarized in Table 1. All the comparisons between the two therapeutic regimens were performed excluding the patients previously treated only on-demand.

In case of three patients the frequency of infusions was reduced by about a third (−29.5%), with a similar considerable mean reduction in the annual recombinant factor VIII (rFVIII) consumption (−30.9%). Four patients had to increase their infusion frequency (mean +14.4%), but even in their case there was a mean annual reduction in rFVIII concentrate used (−12.2%). In the remaining five patients, the frequency of infusions was the same, while also in these cases the use of a PK-driven approach has allowed to reduce the average consumption of concentrate, even if less evidently than what has previously been described (−3.1%).

A subsequent economic evaluation carried out for each of the twelve severe haemophilia A patients included in this analysis, in which we have compared the standard and the PK-driven prophylaxis, showed that an optimized treatment can lead to an annual average saving of E20,525 (−15.8%).

Annual bleeds were reduced in 66.7% of patients (mean 1.9 annual bleeds vs 1.0), with a reduction in on-demand FVIII consumption. In fact, all bleeds were treated with additional doses of concentrate (mean 2000 IU/each bleed). All children start (3/8 patients) or continue (5/8) a physical activity after switching to tailored prophylaxis. Among these three play soccer three times a week, two play basketball three times a week, three swim two/three times a week. Only two adults, the youngest, swim or play five-a-side football, but not constantly. The remaining two have some movement difficulties due to severe arthrosis to knees, ankles and/or hips. Only some traumatic and mild/moderate haematomas were reported by patients during their physical activities.

The aim of this report was to describe our experience in a group of patients with severe or moderate haemophilia A, in which a tailored PK-driven approach, cropped on the patient, and his pharmacokinetic characteristics, made it possible to optimize the treatment without distorting the therapy or changing the previously used factor VIII concentrate.

PK-driven prophylaxis was proved to be an effective approach to treating haemophiliac patients, and its use is recommended by recent ISTH guidelines [6], however since prophylaxis based on clinical characteristics of patients, as ABR or presence of target joints, is commonly applied worldwide, the PK-driven prophylaxis is not even routinely used due to the difficulty in performing this type of analysis in the absence of equipped laboratories, and despite the availability of such devices as *MyPKfit*® or WAPPS-HEMO [7]. Different studies on the use of the *MyPKfit*® device, have recently been published by Megías-Vericat et al. [8] and by Mingot-Castellano et al. [9]. The authors showed the importance of this tool to evaluate the PK in two different populations of patients with severe haemophilia A, already treated with the same concentrate, 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 to improve clinical outcomes and optimize FVIII consumption. This tailored approach could then reduce bleeding rates without significantly increasing the overall cost of FVIII therapy. Similar data was observed in our Italian study published by Pasca et al. [5] in which an economic evaluation was performed in six young subjects with severe haemophilia A, showing this as an achievable and cost-saving approach. The use of a Bayesian model is proven to be effective in establish a tailored regimen, needed to improve the adherence to treatment and to reduce the ABR in a population of thirty-nine haemophilia patients, as reported by Nagao et al. [10].

Even if the recent published researches [11] confirm that the current evidence does not prove that a switch to a different concentrate can increase the development of inhibitors, this could still happen, also in cases of the new EHL products, as reported by Zanon et al. [12]. In this report an unexpected inhibitor appeared in a previous treated patient

(PTP) with severe haemophilia B after a switching to the extended half-life albutrepenonacog-alfa, accompanied by an ileo-psoas haematoma.

A switch must therefore be carried out with caution, when it can lead to an effective benefit for the patient. The reduction of infusion frequency is one of the greatest needs for patients who ask to change their therapy, as occurs when switching to efmoroctocog-alfa that leads to an average reduction in infusions of about one third compared to other products, even if in some cases using a higher average rFVIII dosage each infusion [4]. The same reduction in infusion frequency was obtained in the 25% of our patients, but at the same time a reduction in the annual rFVIII consumption and a reduction in the annual costs were also obtained. Our analysis showed an overall average reduction in concentrate consumption of 15.8% which leads to an equal reduction in costs. The use of *MyPKfit®* to optimize the treatment of our patients has allowed us to obtain this advantage in the FVIII consumption even in cases of patients who have maintained the same infusion frequency. For us it was therefore sufficient to make some changes to the used therapeutic strategies to improve the treatment without resorting to important changes such as switching to another product. In our study the majority of patients were children, and also for then a tailored approach has led to a reduction in FVIII consumption and a consequent saving. Given that children have an accelerated drug clearance and a reduced half-life, our results suggest that the use of a PK-driven prophylaxis may be even more effective in adults whose metabolism is well consolidated and the pharmacokinetic parameters do not change with growth.

Also because in our country both, Advate® and the only commercialized EHL, have the same unit cost (0.65 €/IU), the switch must be supported by a real benefit for the patient since in some cases it may not be supported by a saving. A limitation to our report is the lack of a comparison head to head between Advate® and efmoroctocog-alfa in a same cohort of patients, using a tailored approach for both drugs. Unfortunately at this moment we can only compare the rFVIII consumption based on the PK-driven prophylaxis (octocog-alfa) with a mean rFVIII consumption (efmoroctocog-alfa), based on registration trials. A Bayesian model such as WAPPS-HEMO could be used to perform this comparison, and to evaluate a tailored prophylaxis with all the drugs not only with Advate.

In conclusion we can affirm that the use of a web-based device as *MyPKfit®* may lead the physician to optimize the treatments of haemophilia patients improving a more rational use of available resources, without distorting the therapy and without putting the patient at a useless, albeit rare, risk of inhibitor development.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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All two authors (S.P; E.Z) meet the International Committee of Medical Journal Editors criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval of the version to be published.

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