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Letter to the Editor

rFVIII single-chain in an Italian population of hemophilia A patients: the Veneto experience

Dear Editor,
the replacement therapy with clotting factor concentrates is considered the treatment of choice for patients with hemophilia (PWH), both concentrates of plasma origin and those recombinant are in fact considered safe and effective in preventing or treating bleeding.
Prophylaxis is the gold standard of therapies, especially in patients with severe or severe-moderate hemophilia, but in some cases the compliance of patients is reduced due to the need of frequent infusions (1).
In recent years, in addition to new subcutaneous drugs, such as emicizumab (2), which are bringing an epochal breakthrough to the treatment of PWH, several new standard half-life (SHL) or extended half-life (EHL) concentrates have been marketed (3). These drugs often associated with a tailored treatment, based on the pharmacokinetic profile of each patient, as also recently suggested by the latest guidelines of the World Foundation of Hemophilia (1), have improved the compliance of PWH to therapy, and, in many cases, reduced the annual bleeding rate (ABR) and improved their quality of life (QoL). Thanks to these innovative products, even some severe adult patients, always reluctant to long-term therapies, have accepted to start a prophylactic treatment.
Lonoctocog-alfa (Afstyla®), the first and only developed recombinant FVIII (rFVIII) single chain is one of these new drugs. rVIII-SingleChain is a truncated B-domain rFVIII, which has a high affinity for the von Willebrand factor (vWF) and a high stability (4). These two characteristics of the drug have shown a markedly improved pharmacokinetic profile, when compared with octocog-alfa (5). The protective role of vWF has in fact made it possible to reach a plasma half-life of 14.2 ± 3.7 hours, comparable to that of EHL (6), without resorting to molecular modifications as occurs with glyco-pegylation (PEG) or fusion with the antibody fragments (FC). Here we report our experience with rFVIII single-chain in a population of hemophilia A patients, followed for one year and compared with their previous treatment with octocog-alfa. All data were collected one year retrospectively and one year prospectively in four different Hemophilia Centers (Padova, Vicenza, Castelfranco Veneto and Verona) all belonging to the same Italian region (Veneto). The observation began on the day of the switch to Afstyla®. Twenty-one previously treated patients (PTPs), 10-59 years-old were switched to lonoctocog-alfa. 81% had severe hemophilia A, 5% moderate, while three (14%) were mild subjects. 72.6% were adults (≥14 years). Mean weight was 74.5 kg (range 26-128), with a mean BMI of 25 (range 15.9 – 41.8). The blood group was available only for 11/21 patients, seven of them had group 0. vWF:Ag was reported in 20/21 patients, mean 98.6% (range 55-201). Enrolled patients were 61.9% who previously had been on prophylaxis with octocog-alfa (2nd generation), while the remaining eight were treated only on-demand, among these 50% were severe adult patients. Five PTPs on demand with octocog-alfa were subsequently put on prophylaxis with rFVIII single-chain, three of them were young mild subjects who practiced intense

sporting activity. Overall, the mean of total, joint and spontaneous ABR were respectively decreased after the switch to 27.5%, 34.7% and 62.2%, while the weekly median number of infusions remained unchanged, 2 (range 1-3); as did the median dose infused, 2000 IU (range 1000-4000). The detailed comparison of the ABRs (total, joint and spontaneous) between the two different treatments in each patient is shown in Table 1.

ID	Octocog-alpha				rFVIII single-chain			
	Regimen	AtBR	AjBR	AsBR	Regimen	AtBR	AjBR	AsBR
Pt01	PRO	3	3	0	PRO	1	0	1
Pt02	PRO	3	3	3	PRO	2	1	1
Pt03	OD	3	1	3	OD	9	6	3
Pt04	PRO	0	0	0	PRO	0	0	0
Pt05	OD	2	2	2	OD	1	0	1
Pt06	OD	4	2	3	OD	2	2	0
Pt07	PRO	0	0	0	PRO	0	0	0
Pt08	PRO	0	0	0	PRO	0	0	0
Pt09	OD	0	0	0	PRO	0	0	0
Pt10	OD	6	2	0	PRO	1	1	0
Pt11	PRO	1	0	0	PRO	0	0	0
Pt12	PRO	0	0	0	PRO	0	0	0
Pt13	PRO	0	0	0	PRO	0	0	0
Pt14	PRO	0	0	0	PRO	1	1	0
Pt15	PRO	0	0	0	PRO	1	0	1
Pt16	PRO	0	0	0	PRO	0	0	0
Pt17	OD	4	1	3	PRO	1	0	0
Pt18	OD	1	1	1	PRO	0	0	0
Pt19	PRO	5	3	2	PRO	2	2	0
Pt10	PRO	4	2	2	PRO	0	0	0
Pt21	OD	0	0	0	PRO	5	0	0
Mean		1.71	0.95	0.90		1.24	0.62	0.34

Table 1. Overall comparison of total ABR (AtBR), joint ABR (AjBR) and spontaneous ABR (AsBR) between the two different one-year treatments for each enrolled patient. PRO: prophylaxis; OD: on-demand

In addition to a complete analysis of the data obtained from the comparison between the two regimens, a head-to-head comparison of the 13 prophylaxis performed first with octocog-alfa and then with Afstyla® was evaluated. The results are reported in table 2. Also in this case, the overall mean bleeding decrease in total, joint and spontaneous ABR reaching respectively a reduction of 56.1%, 63.5% and 57.4%, while the dose and the number of infusions remained substantially unchanged. The increase, not statistically significant ($p=0.84$) in the estimated annual consumption of lonoctocog-alfa compared to the previous coagulation factor concentrate (363,160 vs 324,920 IU/year) was due to the physiological weight gain of the younger patients treated in prophylaxis who therefore required a dose increase. No differences were found in terms of number of infusions, dosage and ABR among patients with different levels of plasma vWF:Ag. In the Veneto region the cost of Afstyla® was established at 0.509 euro/IU the same as octocog-alfa, this allowed to maintain a similar expenditure despite the physiological annual increase of consumed units. Prophylaxis is the gold standard of care in patients with severe or moderate-severe hemophilia, but the frequent infusions are often the cause of a reduced compliance (7), therefore even today some adult patients prefer a treatment on demand despite the high number of bleedings and the worsening of their hemophiliac arthropathy. A turning point has been achieved in recent years by the arrival of new drugs which, by increasing the efficacy profile and reducing the number of infusions necessary to obtain it, have been well received by patients who in some cases have even accepted to undertake a prophylaxis, previously always rejected. Afstyla®, the only rFVIII single-chain, is one of these new drugs. Its pharmacokinetic profile was proven similar to that of different EHL (6), with a higher affinity to vWF:Ag and without any molecule modification (5).

	Prophylaxis (N=13) octocog-alpha			Prophylaxis (N=13) rFVIII Single-Chain		
	Dose single infusion (IU/kg)	Estimated annual consumption (IU/kg)		Dose single infusion (IU/kg)	Estimated annual consumption (IU/kg)	
Min	15,6	812,5		15,6	1.425,8	
Max	38,5	5.032,3		44,4	5.032,3	
Mean	27,5	3.249,2		31,6	3.631,6	
	ABR	AjBR	AsBR	ABR	AjBR	AsBR
Min	0	0	0	0	0	0
Max	5	3	3	2	2	1
Mean	1,23	0,85	0,54	0,54	0,31	0,23

Table 2. Comparison head-to-head between 13 prophylaxis with octocog-alpha and lonoctocg-alpha. ABR: annual bleeding rate; AjBR: annual joint bleeding rate; AsBR: annual spontaneous bleeding rate.

Also in our case, this new drug was well accepted by the patients, two severe adults also chose to do prophylactic regimen. In recent years there has been much discussion on which trough level to maintain to ensure the best protection for the patient, but there is no single answer, it depends on the lifestyle, the hemorrhagic phenotype and the personal characteristics of each individual subject. It is therefore important to establish a tailored treatment regardless of the severity of the disease, using the help of pharmacokinetics, as suggested by the latest guidelines of the WFH (1). Intense sporting activity is one of the reasons why it is necessary to maintain a high trough level (8), even in mild subjects. In our case, in fact, three young mild patients were put on prophylaxis with lonoctocog-alfa precisely to allow them to safely practice soccer.

In our study, the overall mean annual bleeding rate was reduced after switching to rFVIII single-chain in the patients who were previously on prophylaxis with octocog-alfa, maintaining a mean of two infusions per week. The expected annual mean consumption calculated for the mean weight of our patients (74.5kg) was lower (269,190IU) than that reported by Simpson et al. (9), calculated for an adult patient weighing 70 kg (322,140 IU) or than that of the other two EHL drugs compared in their study. The increase in annual IU consumed with Afstyla® compared to those with octocog-alfa depended only on the physiological weight gain of the young patients on prophylaxis. Since in our region the cost of the single unit of lonoctocog-alfa is identical to that of octocog-alfa, the costs have also remained similar.

In conclusion, we believe that Afstyla, given its pharmacokinetic characteristics and the peculiar construction of its molecule, which makes it similar to the different EHLs available to clinicians, can be a valid alternative and a first choice in patients in whom we want to improve the prophylactic efficacy of replacement therapy and their adherence to treatment.

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Conflict of Interest
All authors declare no conflicts of interest.