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REVIEW

COMPARISON OF PERSONALIZED AND STANDARD PROPHYLAXIS BASED ON OCTOCOG ALFA IN PEDIATRIC PATIENTS WITH HEMOPHILIA A

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Abstract: Comparison of personalized and standard prophylaxis - based on octocog alfa in pediatric patients with hemophilia A. Studies on a general population (adults and children) demonstrate a statistically significant advantage of personalized over standard prophylaxis in terms of annual bleeding rate (ABR) and annual joint bleeding rate (AJBR) while studies on a pediatric population included insufficiently large populations, however, their results demonstrate a numerical advantage of personalized approach over standard prophylaxis regimen.

Hemophilia A (HA) is inherited as an X-linked recessive disorder characterized by bleeding diathesis due to reduced plasma activity of coagulation factor VIII (FVIII/antihemophilic factor [AHF]) below 50% of the normal level (< 0.5 IU). The classification of severity of HA is determined according to the deficiency of FVIII, expressed as a percentage of the normal level in international units (1 IU refers to the activity of FVIII in 1 mL of normal fresh plasma obtained from blood mixed with 3.2% sodium citrate solution at a ratio of 9 : 1). Normal results are in the range of 50-150% or 0.5-1.5 IU. Types of HA according to the activity of FVIII:

- severe hemophilia A - activity of FVIII < 1% of the normal level (<0.01 IU/mL),
- moderate hemophilia A - activity of FVIII at 1-5% of the normal level (0.01-0.05 IU/mL),
- mild hemophilia A - activity of FVIII at 5-49% of the normal level (0.05-0.5 IU/mL) (1-3).

In Poland, hemophilia A affects 7 in 100.000 people (3). Detailed information on the incidence of hemophilia and other types of bleeding diathesis are recorded by the Institute of Hematology and Transfusion Medicine (IHiT). As of March 2018, there were 2.253 people diagnosed with hemophilia A in Poland. Information on the number of children diagnosed with hemophilia A date back to 2010-2014 (data of the National Health Fund [NFZ]). In 2014, there were 635 children with hemophilia in Poland (4).

Bleeding associated with hemophilia A is characteristic: heavy, prolonged, and delayed with respect to the time of the injury (several hours/days after the injury), and its severity depends on the level of activity of FVIII. As far as severe hemophilia is concerned, bleeding diathesis tends to manifest itself between 1 and 2 years of age in the form of subcutaneous and intramuscular hemorrhage or prolonged bleeding from injured oral mucosa. The annual rate of spontaneous joint bleeding events is 30-40 episodes per year, starting from the age of 3 or 4 years, including knee, elbow and ankle joints (4).

Notwithstanding intense, multi-annual studies of hemophilia-oriented causal treatment, hemophilia continues to be an incurable disease. The treatment

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is based on the replacement of the deficient factor (administration of concentrates of deficient blood-clotting factors) and inhibition of fibrinolysis, i.e. symptomatic treatment which is divided into prevention of bleeding episodes (prophylaxis) and on-demand treatment used for stopping active bleeding (4, 5).

Early long-term prophylaxis with FVIII concentrate regularly given children every three days a week is able to avoid the fall of the FVIII level <1% by significantly reducing ABR and joint arthropathy.

The most common treatment strategy involves regular infusions of FVIII, and in Poland, it is possible to administer one up to three infusions per week for patients aged below 18 years. However, despite the induced prophylaxis, a large number of children and adolescents still experience bleeding episodes, most likely due to excessively reduced levels of FVIII between infusions. As a result, it is necessary to adjust the dosing regimen and the frequency of administration of FVIII on a case-by-case basis. In this case, it is appropriate to use personalized prophylaxis based on the patient's individual pharmacokinetic profile (6).

Personalized prophylaxis is customized to each patient's individual needs. Patients are characterized by different pharmacokinetic profiles, physical activity or hemorrhagic phenotypes. In developed countries, where patients generally enjoy guaranteed access to treatment, the main objective of personalized prophylaxis is to achieve an annual bleeding rate (ABR of 0) and to provide patients with the quality of life (QoL) similar to that of non-hemophilic people (7).

Nearly all clinical guidelines indicate recombined blood-clotting factors as a first-choice option, and this approach is substantiated by a potentially lower risk of transmission of infectious agents, including any pathogens unknown as yet. This recommendation is communicated to all patients, regardless of their age, including in particular those with negative results of tests for HCV, HBV and HIV.

Specific FVIII products available under drug programs and health care agendas are selected based on contract award procedures organized by the Public Procurement Department of the Ministry of Health. In recent years, a contract for the supply of FVIII under the drug program B.1515 'Prophylaxis of bleeding episodes in children with hemophilia A and B (ICD-10 D66, D67)' has been awarded to octocog alfa with respect to a population of newly diagnosed children receiving primary prophylaxis.

Octocog alfa is a glycoprotein composed of 2.332 amino acids with a molecular weight of about 280 kD. Having been administered by infusion to a patient diagnosed with hemophilia, octocog alfa binds to the endogenous von Willebrand factor in the patient's circulatory system. An activated FVIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X into an activated factor X. The activated factor X converts prothrombin into thrombin. Subsequently, thrombin converts fibrinogen into fibrin, and a blood clot can be formed (8).

Objective

Comparison of personalized and standard prophylaxis regimens based on octocog alfa in pediatric patients with hemophilia A.

Materials and methods

The clinical analysis was carried out based on results of studies identified during a systematic review performed according to the following procedure:

- define eligibility criteria for inclusion of studies into the analysis,
- develop/review strategies for a literature search,
- search of medical evidence sources / update the search results,
- identify full texts of scientific reports that could be useful for the clinical analysis,
- select studies based on the eligibility criteria,
- process results of the studies,
- analyze statistical and clinical significance of the results of the studies included in the analysis.

Relevant clinical studies were identified based on a detailed protocol developed prior to a systematic review performed in accordance with the Cochrane Collaboration guidelines (9). The protocol included eligibility criteria for inclusion of studies into the review, search strategy, method of selecting studies and the planned methodology of data analysis and synthesis.

The analysis included clinical studies meeting the following criteria:

- population: children (up to 18 years of age) with hemophilia A, provided with primary or secondary prophylaxis;
- intervention: octocog alfa used in the standard (primary and secondary) prevention of bleeding episodes based on pharmacokinetics (PK-based prevention);
- alternative technologies (comparators): octocog alfa used in the standard primary and secondary prophylaxis;

- methodology: randomized clinical studies, non-randomized controlled clinical studies or pre-test/post-test studies, observational controlled studies or pre-test/post-test studies;
- endpoints: assessment of hemostatic efficacy, rate of bleeding episodes, number of bleeding episodes, number of patients with bleeding episodes, product dose, QoL total adverse events, presence of inhibitor, deaths, total serious adverse events, loss of patients due to adverse events.

The following medical evidence sources were searched for primary clinical studies: Medline (via PubMed), Embase, Biomed Central (via PubMed), The Cochrane Library (Central), registers of clinical studies (ClinicalTrials.gov), Centre for Reviews and Dissemination. The databases were last searched on 29-30 October 2019.

In the first place, efficacy and safety data for pediatric groups (up to 18 years of age) were extracted, and if there were no separate results for a pediatric population, data for a mixed population (children and adults) were gathered. The information was obtained primarily from full-text publications of studies identified during the literature search, and secondly, from conference reports and abstracts.

RESULTS

The core of the clinical analysis covering a comparison of PK-based personalized prophylaxis using octocog alfa and standard prophylaxis using FVIII products. The eligibility criteria were met by 3 studies described in 6 publications:

- Mingot-Castellano 2018 - a multi-center, retrospective, observational pre-test/post-test study comparing the efficacy of Advate in personalized prophylaxis based on pharmacokinetics and previously used standard prophylaxis based on octocog alfa (10);
- Pasca 2017 - a multi-center, retrospective, observational pre-test/post-test study comparing the efficacy of Advate in personalized prophylaxis based on pharmacokinetics (PK) and standard prophylaxis based on octocog alfa (11);
- Valentino 2012 (Valentino 2011, 2012, 2016) - a multi-center clinical trial composed of two phases: a non-randomized phase when all patients received on-demand treatment and a subsequent randomized phase when patients were randomly assigned to a group receiving personal prophylaxis based on octocog alfa (PK-based prophylaxis) or to a group receiving standard prophylaxis based on octocog alfa (12-14).

The results of the clinical analysis are presented below. Results for which a statistically significant difference was determined are given in bold letters in the tables.

The Mingot-Castellano 2018 study

The rate of bleeding episodes

The average ABR was higher to a statistically significant degree for PK-based personalized prophylaxis as compared to standard prophylaxis. The statistically significant differences for the respective endpoint included the total study population ($p = 0.018$) as well as subgroups of patients at the age of less than 15 years ($p = 0.011$). Similar results were obtained for the annual joint bleeding rate (AJBR). A statistically significant advantage of personalized prophylaxis over standard prophylaxis in the total study population ($p = 0.012$) and in a subgroup of patients aged > 15 years ($p = 0.05$) was also observed for this endpoint. Differences in ABR for patients aged <15 years demonstrated numerically the advantage of personalized prophylaxis over standard prophylaxis, and the absence of statistically significant differences may be due to the low number of patients in this subgroup.

The number of patients with bleeding episodes

The authors of the Mingot-Castellano 2018 study did not provide the number of patients who experienced bleeding episodes, however, they reported the number of patients with reduced and increased ABR following PK-based personalized prophylaxis. A reduced rate was reported for 39% of children (the average reduction was -1.4).

The Pasca 2017 study

The number of bleeding episodes

In the Pasca 2017 study, 2 bleeding episodes were reported for a group of 6 children during personalized prophylaxis while 7 bleeding episodes were reported during standard prophylaxis.

The number of patients with bleeding episodes

During personalized prophylaxis, the percentage of patients with bleeding episodes was 33%, and during standard prophylaxis, the corresponding percentage was twice as high (67%).

Quality of life

In the Pasca 2017 study, it was reported that patients were interviewed with a view of determining their QoL. The results of the interview indicated a general improvement in the quality of life, which was associated with a lower number of bleeding

Table 1. The total annual bleeding rate (ABR) (PK-based personalized prophylaxis *vs* standard prophylaxis) as reported in the Mingot Castellano 2018 study.

Population	FU	Personalize prophylaxis		Standard prophylaxis		Statistical analysis	
		N	Mean (SD)	N	Mean (SD)	MD (95% CI)**	P*
Children (≤ 15 years of age), PTPs	12 months	13	0.6 (0.8)	13	0.7 (0.7)	-0.10 (-0.68; 0.48)	0.713
Adults (> 15 years of age), PTPs	12 months	22	2 (2.2)	22	3.1 (2.4)	-1.10 (-2.46; 0.26)	**0.011**
Total, PTPs	12 months	35	1.5 (1.9)	35	2.2 (2.2)	-0.70 (-1.66; 0.26)	**0.018**

*The p-value reported by the authors of the study. **Own calculations; PTPs - previously treated patients.

Table 2. The annual joint bleeding rate (AJBR) (PK-based personalized prophylaxis vs standard prophylaxis) as reported in the Mingot Castellano 2018 study.

Population	FU	Personalize prophylaxis		Standard prophylaxis		Statistical analysis	
		N	Mean (SD)	N	Mean (SD)	MD (95% CI)**	P*
Children (≤ 15 years of age), PTPs	12 months	13	0.3 (0.5)	13	0.2 (0.4)	0.10 (-0.25; 0.45)	0.655
Adults (> 15 years of age), PTPs		22	1 (1.2)	22	2 (1.8)	**-1.00 (-1.90; -0.10)**	**0.05**
Total, PTPs		35	0.7 (1.1)	35	1.3 (1.7)	-0.60 (-1.27; 0.07)	**0.012**

*The p-value reported by the authors of the study.

Table 3. The number of patients with reduced ABR following PK-based personalized prophylaxis as reported in the Mingot-Castellano 2018 study.

Population	FU	n/N (%)	Average reduction in ABR (SD)[a]
Children (≤ 15 years of age), PTPs	12 months	5/13 (39%)	-1.4 (6.0)
Adults (> 15 years of age), PTPs	12 months	11/22 (50%)	-2.6 (1.4)
Total, PTPs	12 months	16/35 (46%)	-2.2 (1.3)

Table 4. The number of patients with increased ABR following PK-based personalized prophylaxis as reported in the Mingot-Castellano 2018 study.

Population	FU	n/N (%)	Average increase in ABR (SD)[a]
Children (≤ 15 years of age), PTPs	12 months	4/13 (31%)	1.5 (10)
Adults (> 15 years of age), PTPs		4/22 (18%)	1.0 (0.0)
Total, PTPs		8/35 (23%)	1.3 (0.7)

[a)] values reported by the authors of the study.

Table 5. The total number of bleeding episodes (PK-based personalized prophylaxis vs standard prophylaxis) as reported in the Pasca 2017 study.

Population	FU	Personalized prophylaxis		Standard prophylaxis	
		N	The number of bleeding episodes	N	The number of bleeding episodes
Children, PTPs	6 months	6	2	6	7

episodes. Three patients associated improved QoL with an increase in their physical activity level. One patient indicated that of greatest importance in terms of improvement of the QoL was the lower number of infusions during personalized prophylaxis. None of the patients wished to return to previous treatment (a standard approach to the prevention of bleeding episodes).

The Valentino 2012 study

Hemostatic efficacy

The hemostatic efficacy of Advate-based prophylaxis was assessed as excellent or good for a similar percentage of bleeding episodes in patients receiving personalized or standard prophylaxis (78% vs 83%).

Table 6. The number of patients with bleeding episodes (PK-based personalized prophylaxis vs standard prophylaxis) in the Pasca 2017 study.

Population	FU	Personalized prophylaxis	Standard prophylaxis
		n/N (%)	n/N (%)
Children, PTPs	6 months	2/6 (33%)	4/6 (67%)

Table 7. Assessment of hemostatic efficacy of Advate in long-term prophylaxis in the Valentino 2012 study.

Population	FU	Assessment result	Percentage of bleeding episodes	
			Personalized prophylaxis	Standard prophylaxis
Children and adults, PTPs	12 months	Excellent	24%	42%
		Good	54%	41%
		Satisfactory	8%	17%
		None	14%	0%
		Unknown	0%	0%

Table 8. The ABR (PK-based personalized prophylaxis vs standard prophylaxis) as reported in the Valentino 2012 study.

Population	FU	Personalized prophylaxis		Standard prophylaxis		Statistical analysis	
		N	Mean (SD)	N	Mean (SD)	MD [95% CI]	p-value
Children and adults, PTPs	12 months	34	1.9 (1.1) / 2.0 (6.9)[a]	32	1.6 (1.2) / 1.0 (3.5)[a]	0.30 [-0.26; 0.86]	p = 0.2588[b] p = 0.1467[c]

[a] median (IQR); [b] p-value for the average (SD; [c] p-value for the median (IQR).

Table 9. The ABR (PK-based personalized prophylaxis vs standard prophylaxis) as reported in the Valentino 2012 study, including the level of adherence – results of a post-hoc analysis.

Population	FU	Personalized prophylaxis		Standard prophylaxis		p-value
		N	Median (IQR)	N	Median (IQR)	
Children and adults, PTPs (adherent[a])	12 months	31	2.0 (4.1)	30	1.0 (2.1)	no information
Children and adults, PTPs (non-adherent[a])	12 months	3	6.9 (10.4)	2	14.0 (23.8)	no information

[a] group of patients receiving ≥ 90% of recommended infusions of the product; [b] group of patients receiving < 90% of recommended infusions of the product.

The rate of bleeding episodes

In the Valentino 2012 study, no statistically significant differences were observed in the rate of bleeding episodes between groups of patients receiving personalized and standard prophylaxis.

The number of bleeding episodes

In a group of 34 patients receiving personal prophylaxis, a total of 141 bleeding episodes and 121 joint bleeding episodes were reported, and in a group of 32 patients receiving standard prophylaxis, a total of 104 bleeding episodes were reported.

The number of patients with bleeding episodes

The difference in the number of patients with bleeding episodes between the two groups included in the comparison, composed of patients receiving personalized and standard prophylaxis in the Valentino 2012, was not statistically significant.

Quality of life

The Valentino 2012 study included an analysis of QoL based on the Health Related Quality of Life questionnaire. Questionnaires administered at each stage of the study (on-demand treatment and personalized or standard prophylaxis) were completed by 57 patients at the age of ≥14 years. No statistically significant differences in the study results were found between the groups of patients receiving personalized and standard prophylaxis (no detailed figures were reported).

Table 10. The total number of bleeding episodes (PK-based personalized prophylaxis vs standard prophylaxis) as reported in the Valentino 2012[a] study.

Population (analysis)	FU	Personalized prophylaxis		Standard prophylaxis		Statistical analysis
		N	The number of bleeding episodes	N	The number of bleeding episodes	
Children and adults, PTPs (ITT)	12 months	34	141	32	104	no information
Children and adults, PTPs (per protocol)	12 months	23	75	30	77	no information

[a)] data from the publication of the Valentino 2016 study (post-hoc analysis).

Table 11. The number of joint bleeding episodes (PK-based personalized prophylaxis vs standard prophylaxis) as reported in the Valentino 2012[a] study.

Population (analysis)	FU	Personalized prophylaxis		Standard prophylaxis		Statistical analysis
		N	The number of bleeding episodes	N	The number of bleeding episodes	
Children and adults, PTPs (ITT)	12 months	34	121[b]	32	no information	x

[a)] data from the publication of the Valentino 2016 study (post-hoc analysis); [b)] all joint bleeding episodes were spontaneous.

Table 12. The number of patients with bleeding episodes (PK-based personalized prophylaxis vs standard prophylaxis) as reported in the Valentino 2012 study.

Population	FU	Personalized prophylaxis	Standard prophylaxis	Statistical analysis	
		n/N (%)	n/N (%)	RR (95% CI)	RD (95% CI)
Children and adults, PTPs (ITT)	12 months	25/34 (74%)	19/32 (59%)	1.24 (0.87; 1.76)	0.14 (-0.08; 0.37)
	12 months	24/34 (71%)[a]	no information	x	x
Children and adults, PTPs (per protocol)	12 months	14/23 (61%)	17/30 (57%)	1.07 (0.68; 1.69)	0.04 (-0.22; 0.31)

[a)] data from the publication of the Valentino 2016 study (post-hoc analysis).

Safety

The studies Mingot-Castellano 2018 and Pasca 2017 reported no safety data. The Valentino 2012 study presented data on the rate of adverse events reported by all patients, regardless of the intervention used (including the study phase when patients received on-demand treatment). During the study period of 18 months, a total of 200 events were observed in 44 patients, and 19 of them were considered to have been associated with the product. Severe events were reported for 11 patients who experienced 14 episodes. One of these events was considered to have been associated with the product. According to information on severe events in patients receiving personalized and standard prophylaxis, no statistically significant differences were determined between the two groups. No patients were lost due to an adverse event in the groups included the comparison. No patients were observed to have developed an inhibitor or die.

DISCUSSION

The aim of the clinical analysis was to assess efficacy and safety of recombined factor VIII (rFVIII) - octocog alfa used for personalized dosing regimen based on PK as compared to the currently used, standard primary and secondary prophylaxis of bleeding episodes in children (up to 18 years of age) with hemophilia A.

Results of the clinical analysis are not sufficiently non-ambiguous to compare Advate-based personalized prophylaxis and the standard prophylaxis. Studies on a general population (adults and children) demonstrate a statistically significant advantage of personalized prophylaxis over standard prophylaxis in terms of ABR and AJBR. For a population composed of only pediatric patients, a numerical advantage of personalized over standard approach was demonstrated, however, it is likely that pediatric groups in the studies were too small for the results to be statistically significant. It should also be noted that patients with hemophilia A require a highly individualized approach. However, the identified studies show that personalized prophylaxis provides for a better adjustment of the dosing regimen and the number of FVIII infusions, which also has a significant impact on patients. The Pasca 2017 study demonstrated a general improvement of the QoL of patients receiving personalized prophylaxis, which was associated with a lower number of bleeding episodes. One patient indicated that of greatest importance in terms of improvement of the QoL was the lower number of infusions during personalized prophylaxis. None of the patients wished to return to previous standard prophylaxis.

The limited number of controlled studies and those providing the basis for an assessment of health effects by comparing them with baseline levels (pre-test/post-test studies) impedes conclusions on the efficacy of individual products as well as the assessment of their relative clinical efficacy.

CONCLUSIONS

Results for PK-based personalized prophylaxis using Advate were obtained from 3 studies. Studies on a general population (adults and children) demonstrate a statistically significant advantage of personalized prophylaxis over standard prophylaxis in terms of ABR and AJBR while studies on pediatric patients included insufficiently large populations, however, their results demonstrate a numerical advantage of personalized approach over standard prophylaxis.

Conflict of interests

The authors declare no conflict of interest.

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