Treatment and prevention of bleeding in adult hemophilia A patients with inhibitor – economic analysis

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Abstract

Hemophilia A is caused by an absence or deficiency of coagulation factor VIII. Patients with hemophilia may experience recurrent spontaneous hemarthroses or internal bleeding. Following the treatment with factor VIII concentrates, patients with hemophilia A may develop alloantibodies to factor VIII, evidence of which is critical to diagnose hemophilia with inhibitor. The primary goal of treatment in patients with hemophilia with inhibitor is a durable inhibitor elimination and the interim goal is to stop the bleeding. The aim of this paper is to compare the effectiveness and costs of on-demand therapy and prophylaxis in patients with hemophilia A with or without inhibitor. We conducted a review of studies. The outcomes of the studies included in the review suggested that the difference in annual bleeding rate (ABR) between prophylaxis and on-demand therapy is less pronounced in patients with inhibitor. Furthermore, one study found no statistically significant difference in ABR between prophylaxis and on-demand therapy in patients aged ≥ 40, although the consumption of coagulation factor was significantly higher in the prophylaxis group. Treatment of patients with hemophilia A is associated with high costs of coagulation factor concentrates and frequent, stressful and painful injections. Therefore, while considering the introduction of prophylaxis in adult patients, it appears advisable to select groups of patients depending on the frequency of bleeding episodes and to determine adequate treatment strategy.

Introduction

Hemophilia A is a disorder caused by an absence or deficiency of coagulation factor VIII (FVIII). Depending on the coagulation factor VIII level, hemophilia is defined as severe (<1% of normal factor level, 0.01 IU/ml), moderate (1%-5% of normal factor level, 0.01-0.05 IU/ml) or mild (5%-50% of normal factor level, >0.05-<0.50 IU/ml) [1]. As a consequence of treatment with factor VIII concentrates, patients with hemophilia A may develop alloantibodies to factor VIII, evidence of which is critical to diagnose hemophilia with inhibitor. Approximately 15-30% of patients with severe hemophilia develop factor VIII inhibitor[2].

In accordance with the *Polish National Health Program for Patient with Hemophilia and Bleeding Diatheses (2012-2018) (Narodowy Program Leczenia Chorych na Hemofilię I Pokrewne Skazy Krwotoczne na lata 2012-2018)* 2,263 patients (adults and children) were registered by *Institute of Hematology and Transfusion Medicine in Warsaw*, Poland (*Instytut Hematologii i Transfuzjologii w Warszawie*) by 17th of September 2013, including 1,071, 331 and 713 with severe, moderate and mild hemophilia, respectively[2].

Recurrent spontaneous hemarthrosis is the major symptom of severe hemophilia. Hemarthrosis results in arthropathy leading to significant decrease in physical activity and even early labor market exit. Patients with hemophilia may also develop severe and life-threatening spontaneous bleeding to internal organs and body cavities (e.g. intracerebral hemorrhage or gastrointestinal bleeding) or excessive bleeding after trauma[2].

Management of patients with hemophilia A

The mainstay of treatment for severe hemophilia A is factor VIII replacement therapy, administered as[2]:

a) **on-demand therapy** – factor concentrate injections given for clinically evident bleeding episodes;
b) **prophylaxis:**

- primary prophylaxis – regular injections of factor concentrates initiated before documented arthropathy has occurred and after second, clinically significant episode of large joint bleed in patients before the age of 3 years to prevent arthropathy;
- secondary prophylaxis – regular factor concentrate injections started after 2 or more bleeds into joint/joints and before arthropathy has occurred;
- tertiary prophylaxis – regular factor concentrate injections initiated after arthropathy has occurred;
- short-term prophylaxis – regular factor concentrate injections, for less than 45 weeks per year, in patients with hemophilic arthropathy to stop recurrent bleeding into a particular joint or to prevent bleeding during physiotherapy;
- perioperative prophylaxis – factor concentrate injections started prior to surgery and continued until healing is achieved to prevent bleeding in the perioperative period[1].

The development of inhibitor to FVIII is considered to be severe complication in patient with hemophilia, as coagulation factors administered as replacement therapy become inactive. The primary aim of treatment in hemophilia patients with inhibitor is a durable elimination of the inhibitor and prevention of bleeding. The therapeutic strategy to eliminate inhibitors is to administrate regular injections of factor VIII concentrates (immune tolerance therapy)[2]. Dosing frequency in immune tolerance induction is varied, starting with frequent and regular doses and ending with protocols involving significantly higher doses[3]. In order to control bleeding episodes, bypassing agents, inducing thrombin generation in plasma, are used despite the presence of inhibitor to FVIII. Currently, two bypassing agents are used, i.e.: activated prothrombin complex concentrates (aPCC, Feiba®) and recombinant activated factor VII (rFVIIa, NovoSeven®)[1].

In 2008 a therapeutic program for bleeding prophylaxis in children was implemented in Poland (*Prevention of bleeding in pediatric patients with hemophilia A and B*). The program is reimbursed by Polish National Health Fund. First therapeutic program for adults (*Program for hemophilia and bleeding diatheses treatment with coagulation factors*), reimbursed by the Ministry of Health,was implemented in 2001. The current treatment program for the years 2012-2018 is a continuation of the program for the years 2005-2011[1]. The program provides on-demand therapy and short-term prophylaxis (a few months or weeks) in adult patients with recurrent bleeding into a particular joint or muscle and who are not eligible to primary or secondary prophylaxis[4]. The aim of this article is to review current clinical strategies for treatment of hemophilia in adults.

Results

Prophylaxis vs on-demand therapy in patients aged 40 years or older

In the clinical trials on patients with hemophilia A without inhibitor, compared to on-demand therapy, prophylaxis was associated with a significant reduction in the frequency of bleeding episodes (including joint bleeds), however, the difference between prophylaxis and on-demand therapy is less pronounced in hemophilia patients with inhibitor[5,6]. In addition, in the clinical trials comparing prophylaxis and on-demand therapy, most patients were children and young adults (aged ≤ 40 years old)[1]. Jackson et al. (*Jackson 2015*) conducted one of the few studies in patients aged 40 years or older[7]. In this observational study prophylaxis was compared with on-demand therapy of severe hemophilia A in patient aged 40 years or older and younger patients. The study included 220 adult patients from Canada, with 70% of patients being exposed to prophylaxis and 27% aged 40 years or older. Hemophilia with inhibitor affected about 15.6% and 35% of younger and older patients, respectively. Annualized bleeding rate (ABR) was considered to be the primary endpoint in the study. Jackson et al.(*Jackson 2015*) revealed statistically significant differences between prophylaxis and on-demand therapy in terms of ABR (4 vs. 12 bleeding episodes/year; p<0.0001) in hemophilia A patients with our without inhibitor, who were aged ≤ 40 years old (Figure 1). There were no statistical differences in older subjects, aged ≥ 40 years old (12 vs. 13 bleeding episodes/year; p=0.866), even though the discrepancy between factor utilization for on-demand therapy versus prophylaxis was observed (560 vs. 3447 u/kg/year, p < 0.001). We sent and inquiry to the authors of the study on the difference between prophylaxis and on-demand therapy with regard to ABR in patients with hemophilia A with inhibitor, but no response has been received. In all patient aged 40 years or older hemophilia A with inhibitor affected about 35% of patients. Therefore, it is likely that in this age group no significant differences between prophylaxis and on-demand therapy in ABR are present both, in patients with and without inhibitors.

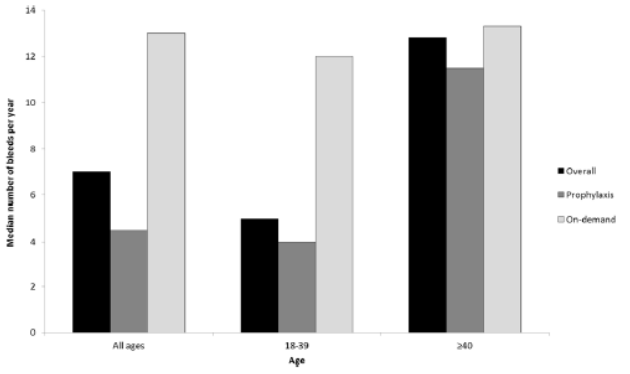

Figure 1. Annualized bleeding rate *Source: Jackson et al.2015*[7]

Comparison of prophylaxis and on-demand therapy for adult patients with hemophilia A with inhibitor

Currently, there are no clear guidelines for the use of prophylaxis in adult patients with hemophilia [4]. These uncertainties are related to the high costs of prophylaxis in patients with arthropathy due to the lack of prophylaxis in childhood and adolescence. The benefits of prophylaxis in this group of patients are limited to reduced bleeding rate, while the influence on inhibition of arthropathy progression is unclear. Scientific evidence shows that secondary prophylaxis in adult patients with hemophilia A aged ≥ 40 years old is ineffective. Hence, the cost of prophylaxis and on-demand therapy in the group of patients aged ≥ 40 years old with hemophilia A with the inhibitor were compared. Data were based on the study *Jackson et al., 2015*[7]. The estimates used median annual number of bleeding episodes in relevant age subgroups.

Two replacement therapies in the prevention of bleeding episodes for patients with hemophilia A with inhibitor are available in Poland: i.e.: NovoSeven® and Feiba®[8,9]. The products are considered to have comparable clinical efficacy[10]. NovoSeven®, according to the product characteristics, is indicated only for the treatment of bleeding and for the prevention of bleeding in patients undergoing surgery or invasive procedures (home therapy available

on request only)[11]. Feiba® is indicated for the treatment and prevention of bleeding (on-demand therapy and prophylaxis)[12]. Considering the comparable efficacy of on-demand therapy and prophylaxis, it is assumed that the only differing cost is associated with the various consumption of coagulation factors.

Prices of coagulation factors were estimated based on Polish National Blood Center data[8] and data from tenders announced by Department of Public Procurement at the Ministry of Health[14]. The Table 1 and Table 2 present estimated prices of one microgram (for NovoSeven®) and a single unit (for Feiba®).

On-demand therapy cost

The treatment costs of a single bleeding episode were estimated taking into account prices depicted in Table 1 and Table 2. The drug doses necessary to control a bleeding episode were adopted on the basis of data reported by *Goszczyńska et al. 2011*[9] *and Lyseng-Williamson and Plosker 2007*[13]. *Lyseng-Williamson and Plosker* summarized data from the following publications: *Dundar et al. 2005*[15], *Hart 2002*[16], *Odeyemi and Guest 2002*[17], *Ozelo et al. 2007*[18], *Plyush et al. 2006*[19], and *Yoo et al. 2007*[20]. The authors of these papers report drug doses used in the general population of hemophilia patients with inhibitor. Estimates of the doses and the costs of Feiba® or NovoSeven® in the treatment of a single bleeding episode are presented in the Table 3. Differences in costs of single bleeding episode treatment with Feiba® and NovoSeven® are about PLN 10 000 in favor of NovoSeven®. Both therapies have similar number of doses required to control a bleeding episode.

Jackson et al. [7] presented results referring to hemophilia patients (with and without inhibitor). Patients aged ≥ 40 years old on prophylaxis had an ABR of 12, while those on-demand use had an ABR of 13. Adult patients aged ≥ 40 years old and on-demand use had an ABR of 12. The estimates of annual costs of on-demand therapy in patients aged ≥ 40 years are depicted in the Table 4.

Cost of prophylaxis

While estimating the annual cost of prophylaxis, doses recommended by the Medical and Scientific Advisory Council (MASAC) [22] were used. Considering the therapeutic indications, it was assumed that in long-term prophylaxis only Feiba® will be used[11,12]. Estimation of the annual cost of prophylaxis made on the basis of MASAC 2013 guidelines is summarized in the Table 5. The recommended dose of Feiba® in the prophylaxis of bleeding is slightly lower in the MASAC 2013 guidelines (three times a week) than in the product characteristics (every other day). However, the dose is still within the range of the recommended dose adjustments and it seems to be in line with everyday clinical practice. Additionally, we performed a non-systematic review of the literature to identify publications reporting prophylactic aPCC consumption in practice. *Negrier et al.* reported significant differences in practical aPCC dosing in prophylaxis[23].

Source	Consumption rFVIIA (µg)	Expenditure (PLN)
Tender ZZP-38/14	13 000 000.00	36 920 000.01
Tender ZZP-159/15	1 800 000.00	5 112 000.00
Tender ZZP-125/15	10 300 000.00	29 252 000.00
Tender ZZP-90/15	11 000 000.00	31 240 000.00
National Blood Center data from year 2013	13 559 000.00	38 507 560.00
Total	49 659 000.00	141 031 560.01
Cost per unit (PLN/µg)	2.84	

Table 1. rFVIIa consumption and expenditure in treatment of hemophilia patients with inhibitor based on data of National Blood Center[14] and Department of Public Procurement at the Ministry of Health[8]

Source	Consumption aPCC (unit)	Expenditure (PLN)
Tender ZZP-130/15	6 000 000.00	22 740 000.00
Tender ZZP-89/15	10 000 000.00	37 900 000.00
Tender ZZP-157/15	5 600 000.00	21 224 000.00
Tender ZZP- 155/14	10 000 000.00	37 900 000.00
Tender ZZP-121/14	1 400 000.00	5 306 000.00
Tender ZZP-36/14	6 000 000.00	22 740 000.00
National Blood Center data from year 2013	8 498 000.00	32 207 420.00
Total	47 498 000.00	180 017 420.00
Cost per unit (PLN/unit)	3.79	

Table 2. aPCC consumption and expenditure in treatment of hemophilia patients with inhibitor based on data of National Blood Center[14] and Department of Public Procurement at the Ministry of Health[8]

		Dundar et al. 2005	Hart 2002	Odeyemi and Guest 2002	Ozelo et al. 2007	Plyush et al. 2006	Yoo et al. 2007	Goszczyńska et al. 2011	Mean
Country		Turkey	Slovakia	Great Britain	Brazil	Russia	South Korea	Poland	na
Mean umber of injections administrated in order to control a bleeding episode	rFVIIa	3.60	2.10	2.30	2.00	1.60	1.70	nd	2.22
	aPCC	4.80	2.00	3.00	3.80	1.70	2.30	nd	2.93
Mean dose required to control a bleeding episode	rFVIIa (ug/kg bw)	204.00	160.00	207.00	190.00	157.00	136.00	219.00	181.86
	aPCC (unit/kg bw)	167,00	105.00	225.00	260.00	135.00	168.00	176.00	176.57
Cost of a single bleeding episode treatment from public payer perspective*	rFVIIa (PLN)	42 009.39	32 948.54	42 627.18	39 126.40	32 330.76	28 006.26	45 098.32	37 449.55
	aPCC (PLN)	45 893.75	28 855.35	61 832.90	71 451.35	37 099.74	46 168.57	48 367.07	48 524.11

Table 3. Costs and drug doses utilized to control single bleeding episode in population of hemophilia patients with inhibitor

bw – body mass, nd – no data, na – not applicable
**taking into account unit price from table 1 and table 2(determined on the basis of National Blood Center data and data from tenders announced by Department of Public Procurement at the Ministry of Health [14]), and assuming a mean body mass of 72.51 kg [21]*

	On-demand therapy using aPCC only	On-demand therapy using rFVIIa only
ABR in subgroup of patients aged ≥ 40years	13.00	13.00
Cost of on-demand therapy (PLN/year)	630 813.38	486 844.16

Table 4. Estimates of annual costs of on-demand therapy for single hemophilia patient with inhibitor

**assuming mean patient body weight of 72.51 kg [21]*

	Dosage based on MASAC 2013	Weekly dosage	Annual cost of drug (PLN)
aPCC	85 unit/kg bw 3 times a week	255.00 unit/kg bw	3 656 532.86

Table 5. Recommended aPCC dosage and costs of long-term prophylaxis per one patient

	Min. weekly dosage	Max. weekly dosage	Annual cost – minimum variant (PLN)	Annual cost – maximum variant (PLN)
aPCC (*Negrier 2016*)	30.61 unit/kg bw	1 075.20 unit/kg bw	438 906.43	15 417 663.24

Table 6. Dosage and cost of prophylaxis per one patient

It is associated with the need for an individual dose adjustment. These values and drug costs are summarized in the Table 6. Given the wide range of doses used in practice, it was assumed that the average annual consumption of Feiba® is equivalent to its consumption determined on the basis of the MASAC 2013 guidelines. It should be noted that in *Jackson 2015* publication, patients aged ≥ 40 years old on prophylaxis were administered higher doses than younger patients. Therefore, it can be assumed that the consumption of coagulation factor (and the cost of prophylaxis) among older patients is higher than the average consumption determined on the basis of MASAC 2013. The Table 7 summarizes the costs of prophylaxis and on-demand therapy, which will be generated by patients aged ≥ 40 years old on prophylaxis. ABR was adopted on the basis of *Jackson 2015* publication. Given the fact that *Jackson 2015* et al. proved no statistically significant differences in the ABR between patients aged ≥ 40 years old on prophylaxis or on-demand therapy, quality of life of these patients may be reduced on prophylaxis due to the frequent dosing (quality of life decrease associated with injections). Prophylactic injections are usually given at least three times a week. *Matza 2013 et al.*[24] presented the influence of injections and infusions on the quality of life in patients suffering from bone metastases. Basing on these results, we assumed that the loss on quality of life due to injections and infusions is comparable in hemophilia patients and in patients with bone metastases. A single injection is associated with a decrease in the patients' quality of life by 0.4%, while the half-hour infusion by 2.3%. Prophylaxis does not guarantee an improvement in general condition in patients aged ≥ 40 years old, and additionally, frequent injections or infusions may be an important factor decreasing the quality of life. The decision whether to administer prophylaxis may be influenced by the difficulties concerning this treatment. This fact may be of particular importance in patients with hemophilia with inhibitor, who tend to receive on-demand therapy[7].

	Value
ABR in the age group aged ≥ 40 years	12.00
Cost of on-demand therapy (PLN per year)	582 289.28
Cost of prophylaxis (PLN per year)	3 656 532.86
Total cost (PLN per year)	4 238 822.13

Table 7. ABR and annual costs of prophylaxis and on-demand therapy of single patient aged above ≥40 years on prophylaxis with Feiba®

Discussion and Conclusions

Patients with hemophilia and related bleeding diatheses represent only a limited part of the general population. However, taking into account the frequent hospitalization need, very high cost of treatment and the difficulties of rehabilitation, it can be stated that hemophilia is a social issue[2]. Hemophilia therapy is associated with high costs of coagulation factor concentrates and frequent, stressful and painful injections[4]. Moreover it often leads to permanent disability which has a huge economic impact on families and the entire society. According to *Forsyth et all* optimal bleeding control therapy decreases pain, prevents further disability and results in better quality of life[25]. We conclude that on-demand treatment is equally effective as prophylaxis in patients aged ≥ 40 years. The Table 8 presents a summary of treatment costs, proving that prophylaxis in hemophilia patients, aged ≥40 years, experiencing an average ABR, compared to on-demand treatment, is associated with several times higher costs. Extrapolation of this age group results from *Jackson 2015* on hemophilia with inhibitor patients allows to conclude that higher costs do not cause a significant improvement of the health state (in patients aged ≥ 40 years, ABR was comparable both on prophylaxis and on-demand therapy). Older subjects with prophylaxis had a higher ABR than younger subjects (12 vs 4). The authors did not provide explanation for ABR age-related differences.

On-demand therapy with NovoSeven® is cheaper than treatment with Feiba®. The difference in the treatment cost for single bleeding episode is about PLN 10 000. It should be noted that prophylaxis, despite its significantly higher cost, does not provide significant improvement for patients aged ≥ 40 years and inconveniences associated with frequent injections (several times a week) may have the opposite effect to that which is intended. Therefore, while considering the introduction of prophylaxis in adult patients, it appears advisable to select groups of patients depending on the frequency of bleeding episodes and to determine adequate treatment strategy (long-term prophylaxis, short-term prophylaxis, indefinite prophylaxis and on-demand therapy)[4].

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	Cost of single patient prophylaxis with aPCC	Cost of single patient on demand treatment with aPCC	Cost of single patient on demand treatment with rFVIIa
ABR in patients aged ≥ 40 years	12.00	13.00	13.00
Cost of acute treatment (PLN per year)	582 289.28	630 813.38	486 844.16
Cost of prophylaxis (PLN per year)	3 656 532.86	-	-
Total cost (PLN per year)	4 238 822.13	630 813.38	486 844.16

Table 8. Summary of costs depending on treatment option in patients aged ≥ 40 years

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