



BUDGET IMPACT ANALYSIS OF INHIBITOR HAEMOPHILIA A THERAPY WITH BYPASSING AGENTS

Konstantin Tachkov, Guenka Petrova
Department of Organization and economy of Pharmacy, Faculty of Pharmacy, Medical University of Sofia, Bulgaria.

ABSTRACT:

The aim of this study is to analyse the budget impact of hemophilia A therapy with either APCC or rFVIIa, in case of persistent inhibitors development. The point of view is that of the Bulgarian health care system for a one-year period.

A budget impact analysis (BIA) was performed following the recommendations of Guideline for Budget impact analysis with some modifications. The analysis is based on combination of literature evidences for both products' efficacy; regulatory requirements for products standard dosage regimens; public expenditures data, and official approved prices of APCC and rFVIIa.

Results show that the yearly per patient cost of therapy with APCC accounts for 162 573 Euro, while treatment with rFVIIa accounts for 377 487 Euro - almost double the cost. If all the patients with inhibitors in each age group exhibit the same number of bleeding events and consume the same maximal dose, the total yearly cost of therapy with APCC will account for 5 621 068,04 Euro and cost with rFVIIa will account for 12 950 344,55 Euro. Therefore, applying APCC instead of rFVIIa would decrease the budget impact by 7.3 million Euro.

In conclusion the treatment of inhibitors hemophilia A with APCC is cost saving for the Bulgarian health care system in comparison with rFVIIa.

Key words: hemophilia, inhibitors, APCC, rFVIIa,

INTRODUCTION:

Hemophilia A and B are rare inherited genetic bleeding disorders appearing in 1 in 5000 to 1 in 30000 males, respectively [1, 2]. Both are caused by missing or defective factor VIII (FVIII) or IX clotting proteins [3]. The main medication to treat hemophilia A is concentrated FVIII product, called clotting factor [4]. Many technological and scientific improvements that increase the safety and efficacy of this clotting factor tremendously have been made in recent years [5, 6]. As a result of the progress, the life span of people with hemophilia has continuously become closer to that of people in the general population [7]. There are many challenges in hemophilia therapy and some are the management of surgical interventions, and development of persistent inhibitory antibodies, especially in patients with severe form of

the disease [8, 9]. People with inhibitory antibodies do not respond to factor concentrate that deteriorates their condition and increases enormously the cost of hemophilia therapy as well as associated complications [10].

Therapeutic guidelines recommend so called bypassing agents for treatment of patients with inhibitors [11]. There are two authorised bypassing agents, such as activated prothrombin complex concentrates (APCC) and recombinant factor VIIa (rFVIIa), that are used for prophylaxis and therapy of acute bleeding in people with high titer inhibitors [12]. APCCs like Factor Eight Inhibitor Bypassing Agent (FEIBA[®]) are made from human plasma and contain variable amounts of clotting factors such as factor VII, factor IX, and factor X [13]. rFVIIa (NovoSeven[®]) is a synthetic product that also has to be administered frequently [14].

A randomised comparison of both products designed to test the equivalence of APCC and rFVIIa came to the conclusion that both products appear to exhibit a similar effect on joint bleeds, but the between patients differences in efficacy observed were not statistically significant [15]. Having in mind the closeness in effect for the majority of patients, two questions arise - how to maintain the therapy at the lowest possible cost for society and how to control the health care budget.

OBJECTIVE:

The aim of this study is to analyse the budget impact of hemophilia A therapy with either APCC or rFVIIa, in case of persistent inhibitors development. The point of view is that of the Bulgarian health care system for a one-year period.

The main question of analysis is "what would the health care budget be if the therapeutic products are dosed according to their short product characteristics (SPC) at the authorized prices" [13, 14].

MATERIALS AND METHODS:

A budget impact analysis (BIA) was performed following the recommendations of Guideline for Budget impact analysis with some modifications [16]. The analysis is based on combination of literature evidences for both products' efficacy; regulatory requirements for products standard dosage regimens; public expenditures data, and official approved prices of APCC and rFVIIa.

Epidemiological data at the national level was collected from the Bulgarian hemophilia association, whereas data on age distribution of patients treated for hemophilia A was obtained from the National health insurance fund [17, 18]. Prevalence of patients with inhibitors was estimated from published evidences [19].

Two scenarios were created and compared. Scenario 1: all patients with inhibitors are treated with APCC, scenario 2 all are treated with rFVIIa. For those scenarios we calculated the cost of pharmacotherapy, assuming that the regular therapy is performed on demand with FVIII products and bleedings according to SPCs dosage regimes of both products.

The cost of therapy is calculated per event per patient

by multiplying the average weight of patients in the age group with the maximal daily dose per day from the SPCs and unit price of each product.

The two scenarios are compared with the current practice. Information for the current practice is taken from the official webpage of the National health insurance fund and Bulgarian Guideline for Hemophilia therapy [18, 20]. It includes data on paid units and expenditures for both products during the last three years.

Efficacy data are taken from the already mentioned randomised comparison and published literature [15, 21]. Prices of both products are from the webpage of the National Council on Prices and reimbursement [22]. All costs are expressed in Euro. Input variables are presented in Table 1.

Table 1. Variables used for the analysis

Variable	APCC	rVIIa	Source
Number of treated patients with hemophilia A	300 app. (279 in 2014)		http://ncphp.government.bg/files/komisia_rare_diseases/Dosieta_RD/D66_0_HeamophiliaA.pdf
Prophylactic dosage regime for frequent bleedings in patients with inhibitors' hemophilia A	70-100 UI/kg one or two times daily 3 times per week	Not recommended	13, 14, 20
Bleeding dosage regime	50-100 IU/kg every 12 hours (max daily dose 200 IU/kg)	90 mcg/kg bolus every 2-3 hour (max daily dose 270 mcg/kg)	20
Cost per unit (Euro)	0.7795 for IU	0.662 for 1 mcg	22
Annual number of bleeds on prophylaxis	7.9	15.8	21
Number of patients with inhibitors and severe hemophilia A	20-30%		20
Number of patients with inhibitors and moderate hemophilia A	10 -15%		
Number of patients with inhibitors and mild hemophilia A	2 - 5%		

RESULTS:

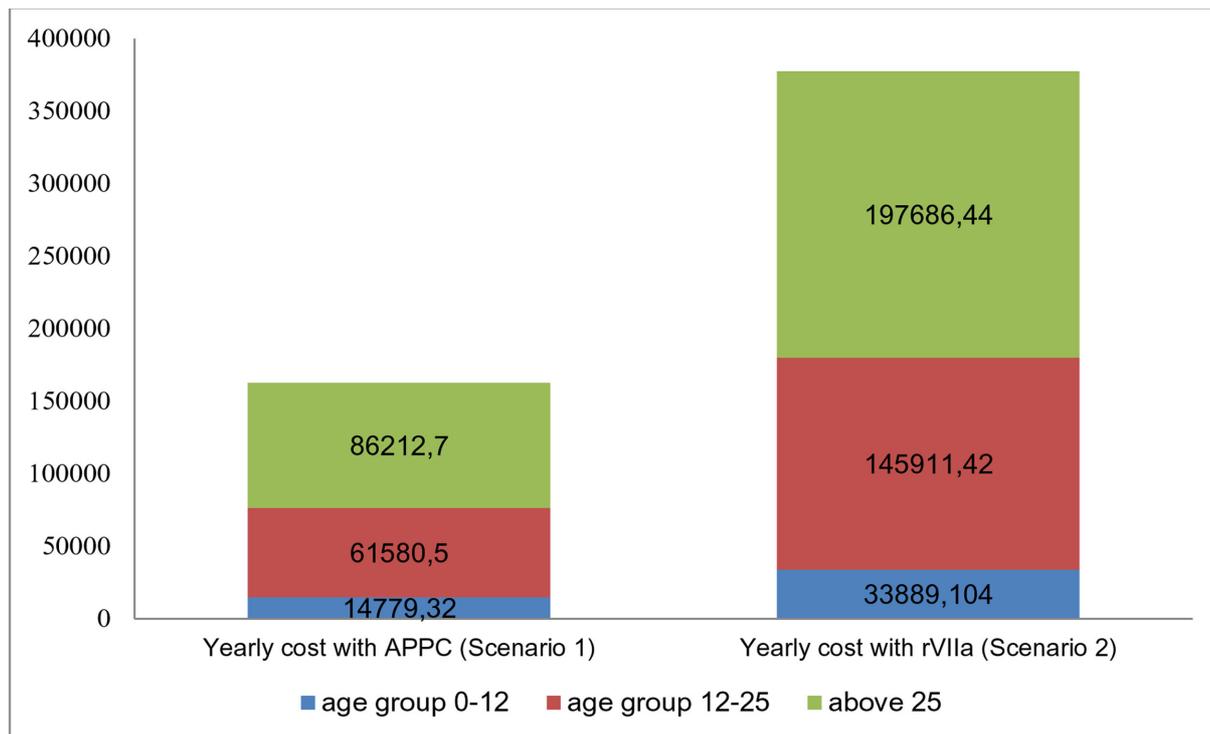
The distribution of patients by age groups, average weight, and cost of therapy per patient with the products under consideration is shown on Table 2. The unit cost per event per patient is lower with the APCC in all age groups.

Table 2. Distribution of patents per age groups and cost of therapy per patient

Age groups	N of patients	Average weight	N of patients with inhibitors (30% of all group)	APCC cost per patient per bleeding event (Scenario 1)	rRVIIa cost per patient per bleeding event (Scenario 2)
0 - 14	58	12	17	1870,80	2144,88
15 - 25	44	50	13	7795,00	9234,90
Above 25	177	70	53	10913,00	12511,80

Literature evidences shows that the average number of bleeding episodes is lower in patients treated with APCC in comparison with rFVIIa [21]. If we assume that in every age group the same number of bleeding events are observed, the yearly per patient cost of therapy with APCC accounts for 162573 Euro, while treatment with rFVIIa accounts for 377487 Euro -almost double the cost. (Figure 1) The latter assumption is made by applying the maximal allowed daily doses for both products.

Fig. 1. Yearly cost of therapy per patient per age group for all bleeding events



If all the patients with inhibitors in each age group exhibit the same number of bleeding events and consume the same maximal dose, the total yearly cost of therapy with APCC will account for 5 621 068,04 Euro and cost with rFVIIa will account for 12 950 344,55 Euro. Therefore, applying APCC instead of rFVIIa would decrease the budget impact by 7.3 million Euro.

Officially published information from the National health insurance fund for the expenditures paid for bypassing agents in the period 2015-2017 is presented on Table 3.

Table 3. Expenditures and number of dispensed doses of bypassing agents

Expenditures for bypassing agents in Euro	2015	2016	2017
EPTACOG ALFA (ACTIVATED)- rFVIIa	2 582 872	3 131 762	2 138 260
NONACOG ALFA – APCC	235 062	356 791	459 310
Paid quantities of bypassing agents			
EPTACOG ALFA (ACTIVATED)- rFVIIa (mcg)	3 901 619	4 730 758	3 230 000
NONACOG ALFA – APCC (IU)	301 554	457 718	635 420

Currently, therapy of hemophilia A with inhibitors is managed with both bypassing agents with the quantities and expenditures share of rFVIIa prevailing. 2017 saw a decrease in sales of rFVIIa, partly covered by an increase in APCC sales but the value of total expenditures for bypassing agents is decreasing. It is also evident that for both products the real expenditures are far below the calculated amount following the recommended doses in SPCs.

DISCUSSION:

This study shows that the treatment of inhibitor

hemophilia with APCC is less costly than the treatment with rFVIIa for the Bulgarian healthcare system. In contrast, real-life practice shows a predominant usage and payment for rFVIIa, which might be discussed as an irrational behavior leading to higher budget impact than necessary. It also shows that the current practice does not correspond to standard dosage regimens, recommended in therapeutic guidelines and leads us to thinking that patients are probably undertreated.

Our results are similar to that of another budget impact analysis performed for the US health care settings [21].

It concludes that the APCC prophylaxis may be cost saving for managing hemophilia patients with inhibitors who bleed frequently and infuse significant quantities of rFVIIa on-demand. In contrast we compare only the on demand regime and come to the same conclusion. Therefore we might suppose that both prophylaxis and on demand regimes are less costly with APCC. Similar are also the results for the health care system in Spain [23]. It calculated that prophylaxis with APCC reduces number of bleeding episodes in severe hemophilia A patients with inhibitors and saved 100 000 Euro per-patient per year, being 16% less costly than on-demand treatment with rFVIIa, for the Spanish NHS.

Applying the principles of cost minimization analysis, the study of Hay et al. concluded that first-line APCC compared to rFVIIa can be a cost-saving alternative for home treatment of mild-to-moderate bleeds in hemophilia patients with inhibitors [24]. Although different methodology is applied the results and conclusions are the same. Cost minimization analysis was also applied by Bonnet et al. in analyzing the cost of patients undergoing major surgery [25]. In this study authors commented that the use of APCC alone or in combination with rFVIIa has emerged as a cost-saving approach. Applying both products still is cost saving for the health care systems.

The cost-effectiveness analysis was applied in the study of Miners A.H. that explores previously published cost-effectiveness analysis of primary prophylaxis vs. treat-

ing on-demand. Authors encourage the conduct of further primary research related to economic aspects of primary prophylaxis [26]. The objective of the study by Carlson et al. was to compare cost and outcome of aPCC and rFVIIa in the treatment of joint bleeds [27]. This study is similar to ours, because it has the same key determinants of cost as prescribed dose, bodyweight and treatment per protocol. It also found that the cost of aPCC was on average lower than rFVIIa.

A lower cost of real practice in comparison to that of corresponding guidelines recommendation was confirmed by an international comparative study of hemophilia cost which included Bulgaria [28]. It might be explained partly with the extremely limited resources of the health insurance fund and applied cost-containment measures, but as authors pointed out the future of this disease is likely to change with the development of new innovative treatments and it will impact future costs related to hemophilia.

The only other economic study of hemophilia in Bulgaria focused on a comparison between the costs of on demand vs prophylaxis dosage regimes [29] and supports the prophylaxis regime as preferential from the point of view of patients and society.

CONCLUSION:

The treatment of inhibitors hemophilia A with APCC is cost saving for the Bulgarian health care system in comparison with rFVIIa.

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Address for correspondence:

Guenka Petrova,
Faculty of Pharmacy,
2 Dunav Str., Sofia 1000, Bulgaria
E-mail: guenka.petrova@gmail.com