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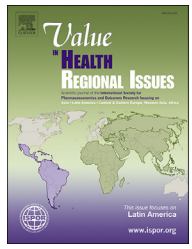

Economic Evaluation

Cost of Patients With Hemophilia A and High-Titer Inhibitors in Colombia

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ABSTRACT

Background: In Colombia, hemophilia is considered a high-cost disease, and hemophilia A with high-titer inhibitors may be responsible for a significant economic pressure on the Colombian health system. **Objectives:** To estimate the direct cost of care for patients with hemophilia A with high-titer inhibitors in Colombia, from the perspective of the health system. **Methods:** A cost-of-illness study was carried out using standard case methodology, which was designed based on literature review and validation by expert consensus. Scenarios were established for adults and children, including cases of prophylaxis, immune tolerance induction, bleeding, and surgery. The frequencies were taken from the official report for Colombia, issued by the High-Cost Account 2017 (reported 2018). The prices were obtained from the list of regulated medicines in the country. The cost estimate is presented with a range of values by weight (between 10 kg and 90 kg). **Results:** The total estimated cost per year for Colombia was US $44 905 252 (between US $32 260 497 and US $58 202 393). The average cost per year calculated for a patient was US $498 947 (between US $358 450 and US $646 693). A total of 99.8% of the estimated cost was directly related to the cost of the coagulation factors and bypassing agents. **Conclusions:** Hemophilia A with high-titer inhibitors is a disease that generates significant pressure on the Colombian health system, mainly linked to the cost of factors and bypassing agents.

Keywords: cost of illness, FVIII alloantibodies, hemophilia A, inhibitors, prothrombin complex concentrates, recombinant FVIIa

Introduction

Hemophilia A is a disease characterized by coagulation factor VIII deficiency (FVIII) and may be classified as mild (level of FVIII activity: >5% and <40%), moderate (FVIII activity ≥1% and ≤5%), or severe (FVIII activity: <1%).[1] In severe cases, patients present spontaneous bleeding in their joints and soft tissues, which can lead to significant complications, such as joint damage and significant disability.[2] Nevertheless, the most important treatment-related complication present in 25% to 30% of patients[3] is the development of inhibitors or alloimmune antibodies.[1,4]

Inhibitors can be low or high titer based on the maximum titers developed by a patient after repeated exposure to FVIII. A person with high-titer inhibitors is someone with a titer ≥5 Bethesda units (BU), whereas a low-titer person is someone with <5 BU.[4-6] The Scientific and Standardization Committee of the International Thrombosis and Hemostasis Society has recommended that inhibitor titers equal to or greater than 5 BU be considered as high titer.[4,6]

These antibodies, especially in cases of high titer, can modify the pharmacokinetics of replacement therapy, reducing the effectiveness of treatment. In addition, even after increasing the frequency and dose of FVIII, in some patients it is not possible to control bleeding episodes, making necessary the use of alternative therapies, immune tolerance induction (ITI) as an option to eradicate inhibitors,[4] or bypassing agents, either activated prothrombin complex concentrate (aPCC) or activated recombinant factor VII (rFVIIa).[7] The presence of high-titer inhibitors against FVIII in patients with hemophilia A has a high impact on clinical and therapeutic aspects of the disease, which in turn translates into an increase in costs for the health system.[8,9]

In Colombia, hemophilia is considered an orphan disease, and because of the existing legislation in the country, the hemophilic population has been granted special access to necessary health

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technologies for disease management.[10] This level of social development has been positive for patients, but at the same time, it has resulted in an important economic effort from the Colombian General System of Social Security in Health. This problem has forced entities such as the High-Cost Account (HCA) to clearly document the frequency, clinical characterization, and outcomes of this disease. In fact, according to this entity's official data reported in 2018, it is known that 1794 hemophilia A patients live in Colombia, of whom 291 (16%) have developed FVIII inhibitors and 90 are classified as high titer.[11] Nevertheless, to date, no studies have revealed the cost of care for these patients. Despite there being only a small group of patients within the universe of this pathology, the estimated cost of care represents a high component of the cost of illness, which is why it is fundamental for the health system to determine the resources and costs of care that are required by this population. Therefore, this study was proposed with the objective of estimating the direct cost of care for patients with hemophilia A with high-titer inhibitors in Colombia, from the perspective of the health system.

Methods

A cost-of-illness study was carried out using the case-type methodology, designed for the Colombian population of children and adults with hemophilia A and high-titer inhibitors.

Perspective of the Study

The perspective of the Colombian General System of Social Security in Health was used, given that the treatment of hemophilia, including complications of inhibitors, is covered in its entirety by the Colombian health system. A time horizon of 1 year was defined.

Reference Case Design

A systematic literature search was conducted to identify the best available evidence for the treatment of hemophilia A with high-titer inhibitors. Based on these results, the theoretical treatment options for this population of interest were constructed. The literature review led to an approximation of theoretical clinical scenarios, including possible therapeutic schemes, doses, and frequencies. With these theoretical cases, the primary group of experts in clinical hematology defined the preliminary cases after 5 rounds of work. Once consensus was reached within the primary group, an external validation exercise was conducted in consultation with an extended group of 8 national experts, which allowed definitive reference cases to be established.

The cases were divided between adult and pediatric populations. In these groups, the costs of prophylaxis using bypass agents, ITI therapy, acute bleeding events, and surgical procedures were estimated. For the cases of prophylaxis and bleeding, the 2 available bypassing agents (rFVIIa and aPCC) were included; for ITI cases, the costs of the factors available in Colombia (recombinant and plasma FVIII) were considered. In addition, reference cases of minor and major surgery were defined. According to different studies that have evaluated surgical events in patients with hemophilia A, the most frequent minor events include tooth extractions, catheter implantation, cataract surgery, and cystoscopy, among others, and major events are represented by different options, among which the most frequent was joint replacement surgery.[12-14] Given the heterogeneity, 3 real cases of patients with hemophilia A with inhibitors were selected to undergo surgery during the study period in one of the comprehensive care hemophilia programs in Colombia. The first case (minor surgery) corresponded to the implantation of a central venous catheter in a child with a body weight of 11 kg, whose cumulative final dose was 45 mg rFVIIa. The second case (major surgery) was a brain hematoma drainage in a child with a body weight of 20 kg, with a cumulative total dose of 180 mg rFVIIa. The last case (major surgery in an adult) was a hip replacement in a patient weighing 65 kg whose cumulative total dose was 600 mg rFVIIa (including the rehabilitation program). These cases were the basis for calculating the cost of minor and major surgery. According to the expert consensus, the bypassing agent used to take the patient to surgery is decided by the hematologist, and the physician is usually inclined toward the bypassing medication with which the patient has been treated with good response; consequently, for the purposes of a conservative exercise, it was assumed that 100% of the patients taken to surgery ($n = 6$) were treated with the agent that by its dosing scheme would represent the highest cost in the Colombian market (rFVIIa).

A general description of each reference case is presented in Table 1, considering the population, body weight, bypassing agent or factor, usual dose, dose adjusted for the presentation of the product, and the estimated time of treatment.

Frequency Estimation

The estimated cost was obtained by multiplying the monetary value of a standard case by its probability of occurrence. This probability was estimated based on 3 combined information sources. The first source of data corresponds to the official information provided by the HCA, in its report on hemophilia in Colombia in 2017.[11] The frequencies or probabilities of occurrence that were not provided in this report were complemented with data from the published scientific literature (frequencies of minor and major surgery; bleeding risk for each type of treatment).[8,12,15,16] Finally, all frequencies were validated by the primary group of expert hematologists and in a round with external experts.

Sources of Price Information

For the estimation of costs of the present study, the prices of the bypassing agents available in the country in their different presentations and those of the recombinant and plasma-derived FVIII for ITI were considered. In Colombia, the prices of these medicines are regulated by the National Price Commission for Medicines and Medical Devices, which determines the maximum sale price charged to the health system. This research was conducted based on the latest update available for these prices (March 2018). The prices of factors and bypassing agents are presented in Table 2. In addition, other cost sources were identified based on average attention from health professionals, examinations, and procedures performed on a group of patients with hemophilia; these costs were estimated based on the experience of the primary group of experts. In Colombia, the fees for these services are contained in a manual of the former Social Security Institute and are adjusted by a percentage with which services are usually contracted. For the purposes of the calculations generated in these other sources, the value stipulated in the Social Security Institute manual plus a 48% adjustment was used (worst-case scenario).

Calculation of the Cost

Direct medical costs were estimated by calculating the cost per event for each reference case, considering dose, frequency, and duration. The calculation of the dose required by a patient was based on the dose per kilogram of weight, adjusted to the final presentation of the product. The costs calculated for each reference case were multiplied by the probability of observed or estimated occurrence of the event for a time horizon of 1 year. To establish the total annual cost, the sum of the total annual costs of

Table 1 – Reference cases.

Reference case	Population	Weight	Medication	Dose	Dose-adjusted FPC	Estimated time of treatment
ITI	Children	10-25 kg	FVIII-R FVIII-P	50-75 IU/kg/ 3 per wk	500-1500 UI/d	1 y, 3 times per wk
	Adults	60-90 kg	FVIII-R FVIII-P		3500-6500 UI/d	
Prophylaxis	Children	10-25 kg	rFVIIa	90-120 μg/kg/ 3 per wk	1-3 mg/d	1 y, 3 times per wk
			aPCC	50-75 IU/kg/ 3 per wk	500-1500 IU/d	
	Adults	60-90 kg	rFVIIa	90-120 μg/kg/ 3 per wk	5-7 mg/d	
			aPCC	50-75 IU/kg/ 3 per wk	3000-7000 IU/d	
Mild/moderate bleeding	Children	10-25 kg	rFVIIa	90-120 μg/kg × 3 dose-days	3-7 mg/d	1 d of treatment per event; 3 average doses
			aPCC	50-75 IU/kg × 3 dose-days	1500-3000 IU/d	
	Adults	60-90 kg	rFVIIa	90-120 μg/kg × 3 dose-days	12-18 mg/d	
			aPCC	50-75 IU/kg × 3 dose-days	10 500-19 500 UI/d	
Severe bleeding	Children	10-25 kg	rFVIIa aPCC	90-120 μg/kg/dose 100-200 IU kg/d Reduces up to 50 IU kg/d	1-3 mg/dose 21 000-25 000 IU in 14 d	14 d of treatment; about 73 doses 14 d of treatment
	Adults	60-90 kg	rFVIIa aPCC	90-120 μg/kg/dose 100-200 IU kg/d Reduces up to 50 IU kg/d	6-8 mg/dose 101 000-142 000 IU in 14 d	14 d of treatment; about 73 doses 14 d of treatment
Minor surgery	Children Adults	10-25 kg 60-90 kg	rFVIIa	90 μg/kg/dose	1-3 mg/dose 6-8 mg /dose	7 d of treatment; up to 45 doses
Major surgery	Children Adults	10-25 kg 60-90 kg		120 μg/kg/dose	1-3 mg/dose 8-10 mg/dose	14-21 d of treatment; 100 doses

aPCC indicates activated prothrombin complex concentrate; FPC, final product concentration; FVIII-P, plasma factor VIII; FVIII-R, recombinant factor VIII; ITI, immune tolerance induction; rFVIIa, factor VII activated.

each reference case was made. Finally, the average annual cost of a patient was estimated, dividing the sum of the total cost over the number of hemophilia cases with high-titer inhibitors for Colombia according to the HCA data.[11] The costs were expressed in dollars, calculated based on the market representative exchange rate issued by the Bank of the Republic of Colombia (average January–October 2018; 1 USD = $2900 Colombian pesos).

Scenario Analysis

The researchers considered the patient's weight to be a factor that could generate an important variability in the estimations. Consequently, the calculations are presented through different ranges of weights, for both the infant population (weight between 10 and 25 kg) and the adult population (weight between 60 and 90 kg). That is, an estimate based on a possible range of values and a central estimate is presented.

Results

Frequencies

According to the HCA 2018 report for 2017, 90 cases of patients with hemophilia A were reported with FVIII high-titer inhibitors in Colombia.[17] The distribution of these patients was divided into the adult population (n = 40; 44%) and pediatric population (n = 50; 56%) based on the distribution reported by the HCA. Of these patients, 51 were registered in prophylaxis, 24 in ITI, and 15 on demand. The frequencies by type of treatment are presented in Table 2.

The HCA report indicated that in patients in prophylaxis, the rate of bleeding was 3.9 events per year,[11] and with this information for this cohort, 78 bleeding events in adults and 121 in the pediatric population were calculated. According to the literature review, prophylaxis is able to reduce the bleeding risk in 70% of on-demand patients[16,18]; consequently, the estimation of the average number of bleeding events per patient on demand is 14 per year. With 15 patients on demand, and with a rate of 14 bleeding episodes per year, 140 events in adults and 70 events in the pediatric population were calculated. In the case of patients in treatment with ITI plus prophylaxis, the bleeding event rates for prophylaxis patients were assumed to be 3.9 events per year, and in the case of patients in ITI or ITI plus on-demand treatment, this rate was estimated to be 7.4 events per year, in agreement with what was reported by Hay and DiMichele[19] in 2012. The severity of the bleeding, in both patients in prophylaxis and on demand, was defined based on the Earnshaw et al[16] study and by expert consensus, with a ratio of 85% (low and moderate) and 15% (severe). The frequencies of estimated bleeding events and surgical events are presented in Table 3.

Because surgical events were not reported in the HCA report, these data were estimated by combining the data reported in the

Table 2 – Patients per treatment type and price of coagulation factors and bypassing agents.*

Reference case	Group	FVIII	rFVIIa	aPCC	FVIII + rFVIIa	FVIII + aPCC	Total
Prophylaxis	Child	9	11	11	—	—	31
	Adult	5	7	8	—	—	20
	Total	14	18	19			51
ITI	Child	9	—	—	—	—	9
	Adult	4	—	—	—	—	4
	Total	13					13
ITI + prophylaxis	Child	—	—	—	2	1	3
	Adult	—	—	—	4	1	5
	Total				6	2	8
ITI + on demand	Child	—	—	—	2	—	2
	Adult	—	—	—	1	—	1
	Total				3		3
On demand	Child	—	4	1			5
	Adult	1	7	2			10
	Total	1	11	3			15
Total		28	29	22	9	2	90

aPCC indicates activated prothrombin complex concentrate; FVIII, factor VIII; ITI, immune tolerance induction; rFVIIa, factor VII activated. Estimates made for 90 patients with hemophilia A with high-titer inhibitors in Colombia. Source: High-Cost Account 2017. Price of coagulation factors and bypassing agents (price per international unit or microgram, Colombia 2018, in USD): FVIII, Plasmatic (UI) $0.401; FVIII—recombinant, (UI) $0.578; rFVIIa (Novoseven; μg), $0.673; aPCC (FEIBA; UI), $0.979.

Table 3 – Frequencies of bleeding events and surgeries (estimated in 90 patients).*

Reference case	Group	rFVIIa	aPCC	Total
Mild/moderate bleeding: patients in prophylaxis	Child	53	50	103
	Adult	34	32	66
	Total	87	82	169
Severe bleeding: patients in prophylaxis	Child	9	9	18
	Adult	7	5	12
	Total	16	14	30
Mild/moderate bleeding: patients in ITI + prophylaxis	Child	11	9	20
	Adult	4	2	6
	Total	15	11	26
Severe bleeding: patients in ITI + prophylaxis	Child	2	1	3
	Adult	1	1	2
	Total	3	2	5
Mild/moderate bleeding: patients in ITI, ITI + on demand	Child	46	23	69
	Adult	20	11	31
	Total	66	34	100
Severe bleeding: patients in ITI, ITI + on demand	Child	8	4	12
	Adult	4	2	6
	Total	12	6	18
Mild/moderate bleeding: patients on demand	Child	43	17	60
	Adult	80	39	119
	Total	124	55	179
Severe bleeding: patients on demand	Child	7	3	10
	Adult	14	7	21
	Total	21	10	31
Minor surgery	Child	2	—	2
	Adult	2	—	2
	Total	4	—	4
Major surgery	Child	1	—	1
	Adult	1	—	1
	Total	2	—	2

aPCC indicates activated prothrombin complex concentrate; FVIII-P, plasma factor VIII; FVIII-R, recombinant factor VIII; ITI, immune tolerance induction; rFVIIa: factor VII activated.

* Estimates made for 90 patients with hemophilia A with high-titer inhibitors in Colombia. Source: High-Cost Account 2017, expert consensus and literature review. The frequencies were estimated according to literature review and validated by expert consensus.

Table 4 – Frequencies of other medical services.*

Item	Supply
1. Health personnel	
Specialized medicine consultation: hematology	12
General dentistry consultation	2
Dentistry consultation: prophylaxis	2
Social work consultation	2
Psychology consultation	2
Specialized medicine consultation: physiatry	2
Specialized medicine consultation: orthopedics	2
Specialized medicine consultation: physical therapy	2
Nutrition consultation	2
Specialized medicine consultation: genetics	2
Nursing evaluations	2
2. Procedures	
Elbows x-ray	2
X-ray of anterior-posterior knee, lateral	1
X-ray knees	1
X-ray of antero-posterior ankle, lateral and internal rotation	2
X-ray of pelvis or coxo-femoral articulation (anterior-posterior, lateral)	1
X-ray of pelvis (hip) comparative	1
3. Tests	
Molecular disease diagnosis (genetic testing)	1
Inhibitor testing—Bethesda assay	3
Hepatitis B surface antigen (HBS Ag)	1
Hepatitis C, antibody (anti-HCV)	1
HIV 1 and 2, antibodies	1
HIV, confirmatory test by western blotting or equivalent	1
4. Therapies	
Integral physical therapy, per session	6
5. Other	
Hepatitis B vaccination	1

HCV indicates hepatitis C virus; HIV, human immunodeficiency virus.
* Average events year by patient. Source: expert consensus.

literature[12-14] and the expert consensus. Based on these criteria, it was established that the surgical event rate was 7 cases per 100 patients per year, so it was estimated that in the cohort of 90 patients with hemophilia A with high-titer inhibitors, 6 surgical events could have been presented in the year 2017, distributed in 3 events in children and 3 events in adults, with 2 major events and 4 minor events, for a proportion of 67% of minor surgeries and 33% of major surgeries. Table 3 shows a synthesis of the frequencies used for the calculation. In a complementary manner, the average frequencies of consumption of other services were documented, such as consultations with physicians of different specialties, physical therapy, occupational therapy, imaging diagnostic tests, clinical laboratory tests, and vaccination. These data were obtained from the activity registry of 3 high-quality programs in the city of Bogotá and validated by clinical experts (see Table 4).

Estimated Costs

Based on the reference case definitions, established frequencies, and prices, the total cost estimate for Colombia was $44 905 252 (between $32 260 497 and $58 202 393). In addition, Table 5 presents the estimated total cost for each reference case (ITI, prophylaxis, bleedings on demand, bleedings in prophylaxis, bleedings in ITI, and surgery) and other medical costs. In each case, a band of possible uncertainty is presented against the estimate. The average cost calculated for a patient was $498 947 (between $358 450 and $646 693). From the estimated cost, it could be established that the coagulation factors or bypassing agents explain 99.8% of the cost in Colombia (bypassing agents: $44 814 577; other costs were $90 675). Table 6 shows the estimated average costs for pediatric patients, adults, and the entire population.

Discussion

Based on the results of the present research, the estimated cost per year of treating hemophilia A patients with high-titer inhibitors in the Colombian health system can range from $32 260 497 to $58 202 393. According to data from the Ministry of Health of Colombia, investment for the health sector in 2018 has been about $15 500 million.[20] Of which, according to our estimate, 0.35% would be committed to 90 patients with hemophilia A with high-titer inhibitors.

Although economic evaluations cannot be extrapolated, it is important to contrast the results with the situation in other countries as a point of reference and discussion. Around the world, different groups have studied the cost of hemophilia and, specifically, the cost of complications of high-titer inhibitors.[8,21,22] In Italy, the COCIS study was conducted and its results published in 2003, including data from 52 patients with hemophilia and high-titer inhibitors. The average age of these patients was 36 years, and cases between 15 and 64 years of age were documented. The costs were calculated from the perspective of the national health system, and an average monthly cost of €18 000 was estimated,[21] which, if projected to an annual growth of 5% (projection to 2018: €37 421), is consistent with our finding of an estimated monthly cost of $41 500.

With data from the Taiwanese national health system (years 2004-2007), research was conducted to establish the cost of hemophilia A with high-titer inhibitors. The results included 37 patients with hemophilia A complicated with high-titer inhibitors, with a median age of 37 years. The median cost of annual treatment of a patient with hemophilia A with high-titer inhibitors was $177 348. If these data were projected with an estimated average growth of 5%, between 2004 and 2018, it is estimated that to date, the estimated average cost for Taiwan would be close to $350 000, a figure that is close to the lower cost of the estimate for Colombia ($358 450). For Taiwan, the authors established that 99.4% of the total cost was explained by the coagulation factors or agents used.[22] In the Italian case, Gringeri et al[21] were also able to establish that 98% of the cost of these patients was explained by the agents or factors used. These studies are consistent with the estimate for Colombia, which found that the cost of the agents or factors explains 99.8% of the total cost of care for the disease.

In August 2014, Armstrong et al[9] published a study to estimate the cost of hemophilia in the context of the health system of the U.S. Department of Defense, between 2006 and 2011, including patients with high-titer inhibitors. This study was conducted with data from medical records of 214 patients, among whom 7 were categorized with inhibitors and all were children between 2 and 11 years of age. The median annual cost was $325 780.[9] In our study, the average cost for the pediatric population was $214 790, whereas the overall average cost was $498 947. According to these authors, patients with inhibitors consume more than 3 times the annual cost of hemophilia A, a situation that can be explained mainly by the cost of the agents used in the treatment with ITI or with prophylaxis. These findings would be consistent with the estimates for Colombia, where prophylaxis and ITI add up to 61% of the total cost. It is worth noting that this behavior may be related to the interest that has been awakened in the scientific

Table 5 – Estimated total cost (USD) of 90 patients with hemophilia A with high-titer inhibitors in Colombia.

Concept	Children (n = 50)			Adults (n = 40)			Total (N = 90)		
	Min	Average	Max	Min	Average	Max	Min	Average	Max
Prophylaxis (n = 51)	2 348 251	4 696 502	7 044 753	9 320 424	12 493 111	16 263 150	11 668 675	17 189 613	23 307 903
ITI (n = 13)	396 945	793 889	1 190 834	1 234 939	1 764 199	2 293 458	1 631 884	2 558 088	3 484 292
ITI + prophylaxis (n = 8)	412 429	824 858	1 237 287	4 120 807	5 417 278	6 788 418	4 533 236	6 242 136	8 025 705
ITI + demand (n = 3)	92 161	184 322	273 848	316 636	450 268	585 217	408 797	634 590	859 066
Low/moderate bleeding, prophylaxis (169 events)	176 495	305 125	387 889	590 310	772 937	1 000 340	766 805	1 078 062	1 388 229
Severe bleeding, prophylaxis (30 events)	613 548	1 222 789	1 741 565	2 502 326	2 944 110	3 371 535	3 115 874	4 166 899	5 113 101
Low/moderate bleeding, demand (179 events)	109 355	202 435	247 024	1 024 151	1 297 512	1 676 230	1 133 505	1 499 947	1 923 254
Severe bleeding, demand (31 events)	396 792	792 147	1 157 348	4 714 592	5 534 979	6 335 263	5 111 383	6 327 126	7 492 612
Low/moderate bleeding, ITI + prophylaxis (26 events)	34 653	60 691	76 550	51 710	65 594	84 745	86 363	126 284	161 295
Severe bleeding, ITI + prophylaxis (5 events)	116 241	232 003	337 714	385 100	454 229	520 487	501 341	686 232	858 201
Low/moderate bleeding, ITI, ITI + demand (100 events)	123 897	225 775	278 083	268 602	342 327	610 397	392 499	568 103	888 480
Severe bleeding, ITI, ITI + demand (18 events)	464 964	928 013	1 350 855	1 347 026	1 581 423	1 810 075	1 811 990	2 509 435	3 160 931
Surgery (6 events. 4 minor, 2 major)	125 111	220 590	316 069	882 360	1 007 471	1 132 581	1 007 471	1 228 061	1 448 651
Other costs	50 375	50 375	50 375	40 300	40 300	40 300	90 675	90 675	90 675
Total	5 461 215	10 739 514	15 690 195	26 799 282	34 165 738	42 512 198	32 260 497	44 905 252	58 202 393

ITI indicates immune tolerance induction; Min, minimum; Max, maximum.

community against the possibility of offering prophylaxis with bypassing agents in patients who develop inhibitors.[23]

The standard of care for patients with inhibitors is inhibitor eradication therapy using ITI.[4] Nevertheless, it has been suggested that a limitation of its use is related to cost, which may limit access and even in high-income countries may be an expensive alternative for the payer.[24] The study published by Berntorp and Shapiro,[1] which investigated whether treatment with ITI was a cost-effective alternative for a lifetime horizon in a patient case of 36 years, assuming the perspective of a third-party payer in the United States, established that the projected cost of the ITI for a life expectancy of 75 years was $4.6 million, whereas the estimated cost for prophylaxis treatments was $15 million and in treatments on demand of $7.3 million.[25] The estimated average annual cost for a patient under treatment with ITI in Colombia was $196 776, which corresponds to almost half the cost of treatment with prophylaxis. Nevertheless, in our environment, there are a number of factors—the generalized perception of being a high-cost treatment, logistical and operational difficulties, and cases of failed therapies, among others[24]—that could explain why, despite it being a cost-effective alternative, only 27% of patients with high-titer inhibitors were treated with this therapy in Colombia in 2017.[11]

The cost of treating cases of bleeding has also been the subject of interest in some studies.[9,21,26] It is worth mentioning the work done in Brazil, in which the direct medical costs of the treatment of episodes of mild and moderate bleeding in children and adults with hemophilia with high-titer inhibitors were evaluated from the perspective of the Brazilian National Health System, between August 2002 and February 2006.[26] In this research, 103 episodes of bleeding were documented in 25 patients with high-titer inhibitors, of which 67 were treated with aPCC and 36 with rFVIIa.

Table 6 – Estimated average cost per patient and type of treatment (USD) of hemophilia A with high-titer inhibitors.

Concept	Children (n = 50)			Adults (n = 40)			Total (N = 90)		
	Min	Average	Max	Min	Average	Max	Min	Average	Max
Prophylaxis (children = 31; adults = 20; total = 51)	75 750	151 500	227 250	466 021	624 656	813 158	228 798	337 051	457 018
ITI (children = 9; adults = 4; total =13)	44 105	88 210	132 315	308 735	441 050	573 365	125 530	196 776	268 022
ITI + prophylaxis (children = 3; adults = 5; total = 8)	137 476	274 953	412 429	824 161	1 083 456	1 357 684	566 654	780 267	1 003 213
ITI + demand (children = 2; adults = 1; total = 3)	46 080	92 161	136 924	316 636	450 268	585 217	136 266	211 530	286 355
Low/moderate bleeding: patient in prophylaxis (events in children = 103; adults = 66; total = 169)	1714	2962	3766	8944	11 711	15 157	4537	6379	8214
Severe bleeding: patient in prophylaxis (events in children = 36; adults = 23; total = 59)	34 086	67 933	96 754	208 257	245 343	280 961	103 862	138 897	170 437
Low/moderate bleeding: patients on demand (events in children = 60; adults = 119; total = 179)	1823	3374	4117	8606	10 903	14 086	6332	8380	10 744
Severe bleeding: patients on demand (events in children = 10; adults = 21; total = 31)	39 679	79 215	115 735	224 504	263 570	301 679	164 883	204 101	241 697
Low/moderate bleeding: ITI + prophylaxis (events in children = 20; adults = 6; total = 26)	1733	3035	3827	8618	10 932	14 124	3322	4857	6204
Severe bleeding: ITI + prophylaxis (events in children = 3; adults = 2; total = 5)	38 747	77 334	112 571	192 550	227 115	260 243	100 268	137 246	171 640
Low/moderate bleeding: ITI, ITI + demand (events in children = 69; adults = 31; total = 100)	1796	3272	4030	8665	11 043	19 690	3925	5681	8885
Severe bleeding: ITI, ITI + demand (events in children = 12; adults = 6; total = 18)	38 747	77 334	112 571	224 504	263 570	301 679	100 666	139 413	175 607
Surgery (3 events in children and 3 in adults)	41 704	73 530	105 356	294 120	335 824	377 527	167 912	204 677	241 442
Other costs	1007	1007	1007	1007	1007	1007	1007	1007	1007
Total	109 224	214 790	313 804	669 982	854 143	1 062 805	358 450	498 947	646 693

ITI indicates immune tolerance induction; Min, minimum; Max: maximum.

The average cost of a mild-to-moderate bleeding event treated with rFVIIa was $7590 and WITH aPCC was $13 500. Of these patients, 55.4% were older than 17 years. These data are consistent with the findings of our study, in which it was possible to estimate that the cost of a mild-to-moderate bleeding event treated with rFVIIa on average was $9218, whereas with aPCC, it reached $14 359 on average. The aforementioned Brazilian authors conducted a cost-effectiveness analysis and concluded that rFVIIa compared with aPCC is more effective and less expensive for the treatment of mild and moderate bleeding in the first line. These data, despite not being extrapolated, indicate that in the Colombian context—according to our costs and assuming the effectiveness data reported by those authors—a similar scenario could be plausible.

In Germany, according to data from 2004, there are about 4000 patients with hemophilia, and the costs for the third payer add up to about €300 million per year, generating a high cost for the system. This result is similar to findings of the present article. Costs for minor and major bleeding were estimated from the perspective of the third payer. The estimated average cost for a child of 15 kg, assuming a rate of 12 bleeding episodes per year, of which 85% were minor and 15% major, was €96 497 and in the case of an adult (75 kg) was €436 823[8]; these projected data at present value would be close to €200 000 in the pediatric population and about €900 000 in adults. Our results are very close to these; for instance, in a child of average weight of 17.5 kg, with 14 events per year (85% mild or moderate and 15% severe), the estimated cost was $198 916, and in the case of an adult of average weight of 75 kg, with 14 events per year (85% mild or moderate and 15% severe), the estimated cost was $657 982. It is clear that the costs cannot be extrapolated, and in this case, there are different sources that can explain the difference, including the design of the study and the reference case raised, among others. Nonetheless, the result is consistent with the economic pressure that these complications generate on the health system of any country.

In addition to what was reported in this study, in 2014 in Colombia, the Institute of Health Technology Assessment studied the budgetary impact on the health system of the use of bypassing agents for the treatment of severe bleeding in patients with hemophilia A with inhibitors, using rFVIIa and aPCC as the basis for treatment. The estimated impact for the first year, assuming a penetration of the agents in the market of 50%, was $10.5 million.[27] These data are close to the estimate made in the present

study, in which the total cost of severe bleeding treated on demand and ITI plus demand was $8 836 562.

It is important to emphasize that cost studies cannot be extrapolated to other countries; however, building case scenarios is useful for other countries and research. The estimated costs found in this investigation provide information on the cost trend as well as different drivers and sources that could be taken into account in other countries. In addition, the results allow for the identification of several factors and sources of cost, which is useful for researchers and decision makers. On the other hand, reference cases not only can be useful for research in the Colombian context but also can be taken as models for similar estimates in other countries. The methodology used in this work can help establish cost estimates for diseases or conditions, using official sources, medical evidence, and clinical experience.

Finally, it is worth noting that this is the first direct cost study of hemophilia A with high-titer inhibitors in Colombia, which establishes a baseline for the country and will serve as a tool for decision makers. It will also allow clinical experts to understand the economic impact on the health system of the clinical decisions made about this group of patients. Despite the mentioned strengths of this study, it is worth noting that because of the accuracy of the information gathered by the HCA, information biases might have occurred that caused errors in the estimates. In addition, we may have underestimated the total cost because our estimate was based exclusively on the indirect cost. A complementary study could include direct and indirect costs and contrast the final results. Nevertheless, based on the validation of the results obtained with clinical experts who know the routines and behaviors of hemophilia programs in Colombia, we believe that the results may be close to the real cost of care for hemophilia A with high-titer inhibitors in Colombia and that they constitute an input for decision makers in the country.

Conclusions

Hemophilia A with high-titer inhibitors is a disease that generates significant pressure on the Colombian health system, mainly linked to the cost of the required factors and bypassing agents, with a total estimated cost for the country of US $44 905 252 and an average cost of US $498 947.[a]

It is estimated that 99.8% of the calculated cost corresponds to coagulation factors and bypassing agents. This evidence will allow the country to continue generating policies to offer access to technologies, under the assumption of system sustainability.

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[a] We would prefer use the US$ to express money in the whole document. Not just in this paragraph.