Cost-effectiveness study of prophylaxis with emicizumab versus bypassing agents in patients with severe hemophilia A in Peru

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Abstract

Setting

Hemophilia is a coagulation disorder that occurs in one in 5000 male births. Patients with untreated severe hemophilia A have hemorrhagic complications, including joint bleeds and decreased survival. Emicizumab is a monoclonal antibody approved by the United States for routine prophylaxis of pediatric and adult patients with severe hemophilia A with factor VIII inhibitors.

Objectives

To perform a cost-effectiveness study of emicizumab prophylaxis for children and adults with severe hemophilia A compared with the current disease management in the Peruvian Ministry of Health and the Social Security Health Insurance.

Methods

The patient transition between medical states was modeled with the Markov methodology, and the lifetime costs and incremental effects of emicizumab compared to current management were estimated. The budget impact of emicizumab was estimated by projecting annual net costs and its five-year present value.

Results

In the Ministry of Health, emicizumab would generate savings between 14.6 and 16.0 per child and 11.8 per adult, in current US$ million. Social Security Health Insurance savings would be 12.8 to 14.9 per child and 40.1 per adult. In addition, this strategy would generate effectiveness gains, measured in quality-adjusted life-years, of 0.36 per child and 0.56 per adult and 0.25 per child, and 0.36 per adult in those respective institutions. The budget impact would be a net annual saving of 12.8 and 15.0 US$ million in those entities.

Conclusion

The current management of hemophilia A is very costly and has health outcomes inferior to those possible with emicizumab. This drug would produce significant savings and better patient health. The Ministry of Health and the Social Health Insurance should implement hemophilia prophylaxis and treatment protocols and finance this drug.

Main messages

- This study demonstrated that emicizumab prophylaxis for patients with severe hemophilia A in Peru is a dominant cost-effective strategy, with health gains and economic savings compared to the current management of patients by the Ministry of Health and the Social Security Health Insurance.
- The lack of knowledge of the actual costs of hospital care of these two institutions and the surrogate use of private costs are limitations of this work. However, cost simulations suggest that the study's main result would not change.
- Similar results would likely be obtained in other countries, with potential medical benefits for the 440 000 hemophilia A patients worldwide in addition to economic savings for the paying agencies.

Introduction

Hemophilia is a generally hereditary bleeding disorder caused by problems in blood coagulation. Hemophilia A accounts for 85% of all cases and is generated by insufficiency of coagulation factor VIII.

About 440 000 people have severe hemophilia A worldwide [1]. Untreated patients have significant bleeding complications, including joint bleeds and decreased survival, with an average life expectancy of 8 to 11 years. In the United States in 2017, the burden of disease caused by severe hemophilia A was estimated to be 0.33 disability-adjusted life-years per 1000 population. Co-authors of this article estimated that there are currently 3000 people with hemophilia in Peru. Of those, only 1002 have an official diagnosis, and two-thirds have a severe form of hemophilia. In 2016, Peruvians would have lost 168.8 disability-adjusted life years per 1000 population due to all causes [2]. Extrapolating the United States (US) ratio, hemophilia would cause in Peru just 0.20% of the US disease burden, although it imposes a much higher percentage expenditure on the health system.

Historically, hemophilia has been treated by periodic transfusion of clotting factors derived from blood plasma or manufactured by genetic recombination. Unfortunately, 5-7% of patients with hemophilia A and one-third of patients with severe hemophilia A develop antibodies that inhibit clotting factors and increase mortality. Patients with high levels of inhibitors are treated with alternative hemostatic agents, such as activated prothrombin complex concentrate or recombinant factor VIIa. Children diagnosed with severe hemophilia A may undergo immunotolerance with the administration of high doses of factor VIII to decrease inhibitor antibodies production. This latter procedure only benefits 60-80% of patients under 18 years of age [3].

Severe hemophilia A is one of the most expensive diseases to treat. In the United States, treating one bleeding episode can cost US$ 50000. Patients with severe hemophilia A receive intravenous factor VIII concentrates several times a week to reduce bleeding. Because of its high cost (between US$ 300 000 and US$ 2.5 million per patient annually), only a few receive prophylaxis with alternative hemostatic agents [4].

A worldwide consensus favors prophylaxis over bleeding treatment with the intermittent infusion of factors to prevent spontaneous bleeding. Still, the Ministry of Health in Peru does not provide prophylaxis for severe hemophilia A and treats bleeds with anti-inhibitor coagulant complex or recombinant activated factor VII donated, according to availability. Within the Social Security Health Insurance, all children with inhibitors receive immunotolerance and prophylaxis with anti-inhibitor coagulant complex. Adults do not receive prophylaxis: their bleeding episodes are mainly treated with anti-inhibitor coagulant complex (90%) or by a second line with activated factor VII (10%).

The monoclonal antibody emicizumab (Hemlibra®), approved in 2017 by the Food and Drug Administration, functions as a cofactor for factor VIII. In patients on inhibitors, prophylaxis with emicizumab showed an 87% reduction in bleeding compared with patients without prophylaxis. Two-thirds of patients on prophylaxis were free of bleeding during one year. In patients without inhibitors, the effects were even more favorable. Weekly subcutaneous application of emicizumab facilitates patient adherence, reduces bleeding and hospitalizations, and improves the quality of life. The current evidence recommends that emicizumab should be indicated for hemophilia A prophylaxis with and without inhibitors. However, such a decision should be based on a cost-effectiveness economic evaluation to determine whether the incremental health benefits associated with the use of emicizumab justify its incremental cost.

This study sought to determine the cost-effectiveness of emicizumab as prophylaxis for patients with severe hemophilia A. This treatment was compared with current therapeutic alternative schemes in Peru for adults and children covered by the Ministry of Health and Social Security Health Insurance. Treatment alternatives for severe hemophilia A patients included prophylaxis (with anti-inhibitor coagulant complex or recombinant activated factor VII) or no prophylaxis.

Few international cost-effectiveness studies compare prophylaxis with treating bleeding episodes for hemophilia. Table 1 shows these studies, with a summary of the literature review. The evidence shows incremental cost-effectiveness ratios within acceptable ranges for incorporating new technology into

Table 1. Summary of major published studies on the cost-effectiveness for managing severe hemophilia A.

Reference	Country	Type of hemophilia	Intervention	Incremental cost per year (US$)	Incremental effectiveness (QALYs)	ICER (US$ per QALY)
Miners 2009 [5]	United Kingdom	Severe hemophilia A	Prof. FVIII versus FVIII on demand	214 000	5.60	86 000
Farrugia *et al.* 2013 [6]	United States	Severe hemophilia A	Prof. FVIII versus FVIII on demand	413 000	6.06	71 000
Earnshaw *et al.* 2015 [7]	United States	Severe hemophilia A with inhib.	Prof. with alternative hemostatic agents versus on-demand alternative hemostatic agents	-1 637 240	9.90	Emic = DS
Institute for Clinical and Economic Review [8]	United States	Severe hemophilia A in >12 years with inhib.	Prof. with alternative hemostatic agents (50:50%) vs. emicizumab	-70 960 466	0.20	Emic = DS
	United States	Severe hemophilia A in <12 years with inhib.	Prof. with alternative hemostatic agents (50:50%) vs. emicizumab	-78 528 265	0.38	Emic = DS
	United States	Severe hemophilia A in >12 years with inhib.	On-demand alternative hemostatic agents versus prof. with emicizumab	-8 913 222	0.91	Emic = DS
	United States	Severe hemophilia A in <12 years with inhib.	On-demand alternative hemostatic agents versus prof. with emicizumab	-10 000 971	2.39	Emic = DS

QALYs: quality-adjusted life-years; ICER: Incremental Cost-Effectiveness Analysis; Emic: DS; FVIII: coagulation factor VIII; Prof.: prophylaxis; Inhib.: Inhibitors.
Source: Prepared by the authors of this study.

their respective countries' financing or insurance regime and shows a reduction in disability and increased patient productivity. Only one study with inhibitors in prophylaxis compares the use of this new drug in patients with prophylaxis and alternative hemostatic agents or with on-demand treatment [8]. It concluded that emicizumab reduces annual medical costs per patient by US$ 1.9 million among patients older than 12 years and by US$ 720,000 in younger than 12 years. It also found that emicizumab prophylaxis compared with on-demand treatment or prophylaxis with alternative hemostatic agents could be cost-saving. In addition, emicizumab is more effective and allows a lower cost reduction in disease burden than the other management strategies.

Methods

Design

A cost-effectiveness analysis was performed from a payers perspective (Ministry of Health or Social Security Health Insurance), using a model that simulates the transition of patients between different medical states using the Markov methodology. The model was implemented with the TreeAge program to simulate the natural history of a hemophilia patient in Peru.

Two scenarios were formulated: the "base scenario", which represents the current situation in the Ministry of Health and the Social Health Insurance, and the "project scenario", which represents the adoption of emicizumab prophylaxis in the two institutions. In both scenarios, children (under 15 years of age) in the Ministry of Health and the Social Security Health Insurance receive prophylaxis. This strategy is done with an anti-inhibitor coagulant complex in the base scenario and emicizumab in the project scenario. Likewise, adults covered by the Ministry of Health do not receive prophylaxis in any scenarios. In the Social Security Health Insurance, the base scenario contemplates that adults receive prophylaxis with anti-inhibitor coagulant complex, while in the project scenario, this is done with emicizumab. Additionally, both scenarios contemplate performing immunotolerance to children that present inhibitors in some instances. Table 2 summarizes the design elements described above.

A budget impact analysis was also performed for the Ministry of Health and the Social Security Health Insurance. i.e., the additional annual cost associated with emicizumab as a prophylactic scheme in these two institutions. For this purpose, the costs per patient were multiplied by the annual number of patients who would use emicizumab for severe hemophilia A prophylaxis. It was assumed that initiation of emicizumab

Table 2. Type of prophylaxis and pharmacological treatment in base and project scenarios for children and adults from Ministry of Health and Social Security Health Insurance.

	Type of prophylaxis and pharmacological treatment						
Intitutions and scenarios	**Inmunotolerance**	**Prof. with anti-inhibitor coagulant complex**	**Prof. with emicizumab**	**Mild bleeding Tx with anti-inhibitor coagulant complex**	**Severe bleeding Tx with anti-inhibitor coagulant complex**	**Mild bleeding Tx with anti-inhibitor coagulant complex or FVIIa**	**Severe bleeding Tx with anti-inhibitor coagulant complex or FVIIa**
Ministry of Health							
Adults							
Base				√	√	√	√
Project			√	√	√	√	√
Children							
Base	√	√		√	√	√	√
Project	√		√	√	√	√	√
Social Security Health Insurance							
Adults							
Base		√		√	√	√	√
Project			√	√	√	√	√
Children							
Base without immunotolerance		√		√	√	√	√
Base with immunotolerance	√	√		√	√	√	√
Project without immunotolerance			√	√	√	√	√
Project with immunotolerance	√		√	√	√	√	√

FVIIa: factor VII activated; √: drug is included; Prof.: prophylaxis; Tx.: treatment.
Source: Prepared by the authors of this study.

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prophylaxis occurs at two years in children and 18 years in adults. The horizon of the cost-effectiveness study was 16 years for children and 52 years for adults. The horizon of the budget impact analysis was five years. A literature review concludes a lack of knowledge regarding the annual number of bleeds in patients with severe hemophilia A [8]. Therefore, the Institute for Clinical and Economic Review performed simulations on the number of bleeds [8]. The authors obtained an estimate of the average number of annual bleeds in children and adult patients from Peruvian experts to fill this gap. Although the literature reports an average duration of immunotolerance of 26.2 months until complete tolerance is achieved, the national experts reported that this usually lasts nine months in Peru. Since the dosage of emicizumab is based on the patient's weight, in consultation with the experts, we assumed that the average weight of a child is 35 kilograms and 70 kilograms for adults. We also specified the posology by noting the dose and frequency of administration (Table 3).

Costs

To define the characteristics of prophylaxis, doses, amount of bleeding, and types of treatment of critically ill patients, we collaborated with a committee of Peruvian experts in hemophilia, all of whom participated as co-authors of this article. The estimated annual costs of drugs consumed by patients with severe hemophilia A are shown in Table 3. The emicizumab costs considered the current selling price in addition to a

Table 3. Annual drug costs consumed by patients with severe hemophilia A (US$).

Drugs by type of patient	Presentation	Amount	Base scenario				Indication
			Price (a)	Total annual cost	Annual cost per cycle	Annual cost per cycle with 20% discount (b)	
Cost of prophylaxis							
Adult (h)							
Emicizumab	105 mg	56	7262	406 646	7820	6256	(c)
Anti-inhibitor coagulant complex	500 IU	936	1461	1 367 777	26 303	N/A	(d)
Children							
Emicizumab	105 mg	4	7262	29 046	N/A	N/A	(e)
	60 mg	48	4149	199 173	N/A	N/A	(e)
	N/A	N/A	N/A	228 220	4389	3511	Total (e)
Anti-inhibitor coagulant complex	500 IU	468	1 461	683 888	13 152	N/A	(f)
Children with ITI							
PLASMA FACTOR VIII	250 IU	1916	89	170 163	3272	N/A	(g)
Emicizumab	105 mg	4	7262	29 046	N/A	N/A	(e)
	60 mg	48	4149	199 173	N/A	N/A	(e)
	N/A	N/A	N/A	228 220	4389	3511	Total (e)
Anti-inhibitor coagulant complex	500 IU	468	1461	683 888	13 152	N/A	(f)
Bleeding costs (l)							
Adult							
FVIIa	2 mg	46	3365	154 813	N/A	N/A	(h)
Anti-inhibitor coagulant complex	500 IU	140	1461	204 582	N/A	N/A	(i)
Children							
FVIIa	2 mg	31	3365	104 330	N/A	N/A	(j)
Anti-inhibitor coagulant complex	500 IU	70	1461	102 291	N/A	N/A	(k)

ITI: with immunotolerance; IU: international units; (a): Roche Peru data; (b): Discount only for Roche Peru products; (c): Two ampoules of 105 milligrams per week for the first month, then one ampoule of 105 milligrams per week; (d): 3000 international units three times a week; (e): One 105 milligram ampoule per week the first month, then one 60 milligram ampoule per week; (f): 1500 international units three times a week; (g): 100 international units every other day for nine months. Immunotolerance should be used; (h): Cost of prophylaxis only for Social Security Health Insurance. The Ministry of Health does not perform prophylaxis in adults and only treats bleeding; (i): 100 international units per kilogram every 12 hours for five days; (j): 90 micrograms per kilogram every three hours on the first day and then decrease according to bleeding; (k): 120 micrograms per kilogram every three hours on the first day and then decrease according to bleeding; (l): Each bleeding lasts one cycle.
Total (e) Is the sum of the drugs.
N/A: not applicable.
Source: Prepared by the authors of this study.

Table 4. Pharmaceutical and other benefit costs (US$) in in base scenario (*Clínica Ricardo Palma*) and *Hospital Nacional Dos de Mayo* scenario (US$).

Drugs by type of patient	Severe bleeding costs (a)	Mild bleeding costs (a)	Frequency	Severe bleeding costs	Mild bleeding costs
Base scenario: *Clínica Ricardo Palma*					
Adults					
FVIIa	157 552	154 870	90%	N/A	N/A
Anti-inhibitor coagulant complex	207 321	204 639	10%	162 529	159 847
Children					
FVIIa	107 070	104 388	90%	N/A	N/A
Anti-inhibitor coagulant complex	105 030	102 348	10%	106 866	104 184
Minimun scenario: *Hospital Nacional Dos de Mayo*					
Adults					
FVIIa	155 034	154 824	90%	N/A	N/A
Anti-inhibitor coagulant complex	204 803	204 593	10%	160 011	159 801
Children					
FVIIa	104 552	104 342	90%	N/A	N/A
Anti-inhibitor coagulant complex	102 512	102 302	10%	104 348	104 138

FVIIa: Factor VII activated; (a): Bleeding costs by other health benefits; N/A: not applicable.
Source: Prepared by the authors of this study.

simulation with a 20% discount. The Roche laboratory in Peru provided both the price and the discount. We considered nine months of use to estimate immunotolerance costs in children. For the costs associated with the care received during bleeding states (mild or severe), the price lists of two hospitals with experience in treating hemophilia were analyzed: the *Hospital Nacional Dos de Mayo* and the *Clínica Ricardo Palma*. Considering that the values of public hospitals are heavily subsidized, it was decided to base prices from *Clínica Ricardo Palma*, a private establishment, since the latter would be closer to the actual cost (Table 4). In addition, a simulation was carried out using the costs of the *Hospital Nacional Dos de Mayo*.

Concerning prophylaxis and bleeding treatments, we included drug costs only with the information provided by hematologists specialized in hemophilia and considered an efficient use of emicizumab, taking into account its presentation. We did not include costs of human health resources, such as physicians, nurses, and assistants, because we consider them marginal compared to drug costs. This consideration aligns with published literature (e.g., Earnshaw et al. [7]). The annual costs of caring for patients with severe hemophilia A by an institution are presented in Table 3. The pharmacological components are specified in Table 4. All monetary figures were expressed in *soles* and US dollars on December 31, 2019.

Effectiveness

To be consistent with the pharmacoeconomic evidence on severe hemophilia A, we measured effectiveness in terms of gains in quality-adjusted life-years. Since no information on this measure is available in Peru, we used quality-adjusted life-years reported by the Institute for Clinical and Economic Review [8] for the health states that noted: 'severe bleeding' 0.54, 'mild bleeding' 0.66, 'no bleeding' 0.82 [8].

Pharmacoeconomic evaluation

Using the Markov methodology, the formulated model simulated how hemophilia patients transit with different probabilities (Table 5) between four different health states (Figure 1) in consecutive one-week cycles over time. In each of the four states (e.g., "no bleeding"), the patient has a certain probability of remaining in that state until the next cycle, and three other probabilities of changing state during the cycle (e.g., "death," "mild bleeding," or "severe bleeding").

We considered two scenarios: the base scenario, which corresponds to the current management of hemophilia patients in the Ministry of Health and the Social Security Health Insurance; and the project scenario, which considers emicizumab prophylaxis for three types of patients: adults with inhibitors, children with inhibitors and no immunotolerance, and children with inhibitors and immunotolerance. This event analysis aligns with the Institute for Clinical and Economic Review [8] in their cost-effectiveness study of emicizumab [8]. The time horizon for adults was 52 years (equivalent to the life expectancy for hemophilia A and B patients reported in an English study) and 16 years for children [9]. The model implemented in the TreeAge computer program considered four excludable states: no

Table 5. Transition probabilities.

	Social Security Health Insurance		Ministry of Health	
Transition probabilities	**Emicizumab**	**Another prophylaxis**	**Emicizumab**	**Another prophylaxis**
Adults with inhibitors				
No bleeding	0.96149	0.88457	0.96149	0.84610
Mild bleeding	0.03462	0.10385	0.03462	0.13846
Severe bleeding	0.00385	0.01154	0.00385	0.01538
Death	0.00005	0.00005	0.00005	0.00005
Children with inhibitors without ITI				
No bleeding	0.98067	0.88452	0.98067	0.84606
Mild bleeding	0.01731	0.10385	0.01731	0.13846
Severe bleeding	0.00192	0.01154	0.00192	0.01538
Death	0.00010	0.00010	0.00010	0.00010
Children with inhibitors with ITI				
No bleeding	0.98067	0.88452	0.98067	0.84606
Mild bleeding	0.01731	0.10385	0.01731	0.13846
Severe bleeding	0.00192	0.01154	0.00192	0.01538
Death	0.00010	0.00010	0.00010	0.00010

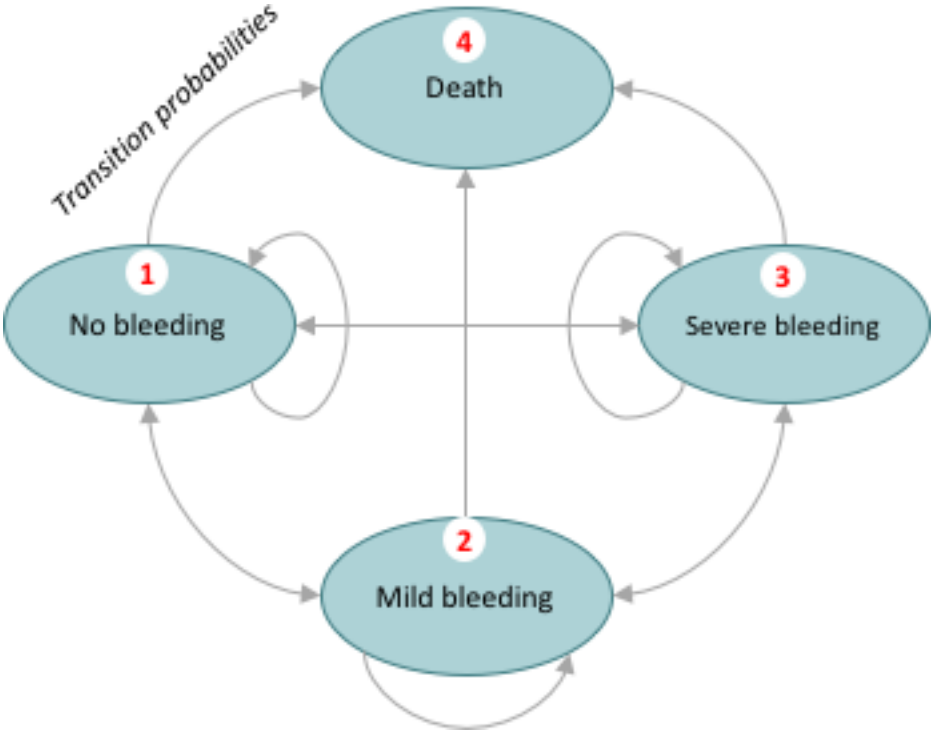
ITI: immunotolerance.;
Source: Prepared by the authors of this study.

bleeding, mild bleeding, severe bleeding, and death; and eight transition probabilities.

Both costs and effectiveness in future years were discounted to present value, using a real annual discount rate of 3% consistent with the only other cost-effectiveness analysis published from the payer's perspective [8].

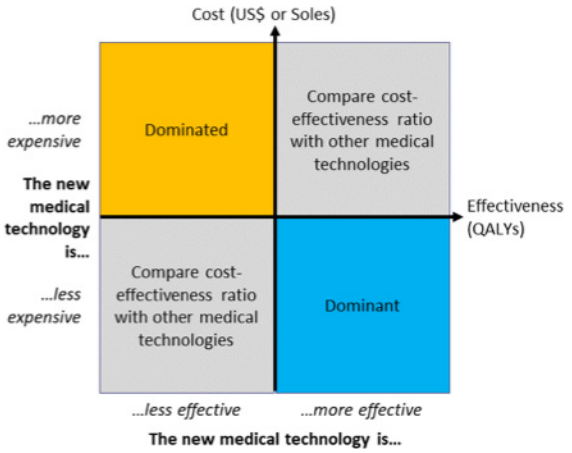
The values resulting from the Markov model (emicizumab prophylaxis scenarios) were compared with their respective base scenarios for the Ministry of Health and the Social Security Health Insurance. Thus, three comparative pairs were formed (base scenario versus project scenario) for the Ministry of Health and three for the Social Security Health Insurance: one

Figure 1. Diagram of states and transitions in patients with severe hemophilia A in the Markov model.



Source: Prepared by the authors according to the model proposed by the Institute for Clinical and Economic Review [8].

Figure 2. Interpretation of the results of a cost-effectiveness study.



QALYs: Quality-adjusted life-years.
Source: Prepared by the authors of this study.

for adults with inhibitors, another for children with inhibitors without immunotolerance, and another for children with inhibitors with immunotolerance. The following assumptions were taken into account for the construction of the model: a) Patients with severe hemophilia A (less than 1% of standard clotting factor VIII). b) The average age of initiation of emicizumab prophylaxis in children is two years and in adults 18 years. c) The number of annual bleeding episodes in the baseline scenario for the Ministry of Health was eight, and for the Social Security Health Insurance was six. d) The number of annual bleeding episodes in the project scenario (in the Ministry of Health and the Social Security of Health Insurance) was one in children with inhibitors with and without immunotolerance and two in adults with inhibitors. e) In cases of bleeding, the additional costs of bed days, examinations, and follow-up medical consultations were considered. f) All cases that presented bleeding were treated with alternative hemostatic agents (current scheme).

For evaluating results, we calculated the present values of total costs; incremental costs (comparing the base and project scenario); effectiveness in quality-adjusted life-years; incremental effectiveness in quality-adjusted life years; and the incremental cost-effectiveness ratio in US dollars per quality-adjusted life-years. This ratio is interpreted according to its location in the quadrants of Figure 2.

The new technology improves the patient's health status and reduces costs in the ideal case. This option is called the "dominant" strategy because it is unambiguously desirable. The undesirable case (when it decreases health status and increases costs) is the "dominated" strategy. Cases in which the new technology improves health status but increases costs or worsens health status but decreases costs should be compared with other medical interventions to determine their relative merit.

Finally, simulations were performed with the model considering reductions in the price of emicizumab.

Budget impact analysis

The present value of the incremental cost for the project scenario represents the savings or increased expenditure (negative or positive incremental cost, respectively) of the total possible cycles for a patient. This present value considered a weekly cost of prophylaxis of US$ 830 for a child and US$ 2707 for an adult. These values, multiplied by the number of child and adult patients, yielded estimates of the annual savings or increased expenditure and the present value over a five-year horizon. This value represents the impact on the budget currently allocated by the Ministry of Health or Social Security Health Insurance to adopt a prophylaxis policy with emicizumab. The impact would be favorable if this new policy would generate budgetary savings or unfavorable if it would require a larger budget. Authorities with decision-making power to adopt emicizumab prophylaxis need to know these results.

In the budget impact analysis we also consider a reduction in the number of future hospitalizations and in their respective costs, but we do not consider adverse events associated with the use of emicizumab since these are infrequent and with relatively minor consequences in the health of the patient.

Results

In both the Ministry of Health and the Social Security Health Insurance, we found that emicizumab proved to be the dominant strategy. In contrast, the dominated alternative strategies included prophylaxis with anti-inhibitor coagulant complex in children and adults, with or without immunotolerance (Table 6).

Compared to the current Ministry of Health strategy, prophylaxis with emicizumab would generate per patient US$ 42.1 million savings for children with inhibitors without immunotolerance, US$ 41.1 million for children with inhibitors and with immunotolerance, and US$ 21.0 million for adults with inhibitors. Moreover, emicizumab would also generate savings in the Social Security Health Insurance. These would be US$ 50.5 million for children with inhibitors and without immunotolerance, US$ 58.9 million for children with inhibitors with immunotolerance, and US$ 11.2 million for adults with inhibitors.

In the Ministry of Health, prophylaxis with emicizumab would generate an effectiveness gain per patient compared to the current strategy. This gain would be 0.36 quality-adjusted life-years per child with inhibitors and without immunotolerance and 0.56 quality-adjusted life-years per adult with inhibitors. In the Social Security Health Insurance, prophylaxis with emicizumab would also generate effectiveness gains compared to the current strategy for managing patients with severe hemophilia A. This difference would be 0.25 quality-adjusted life-years per child with inhibitors with and without immunotolerance and 0.36 quality-adjusted life-years per adult with inhibitors.

Regarding the incremental cost-effectiveness analysis, emicizumab is a dominant strategy in the Ministry of Health and the

Table 6. Cost-effectiveness analysis in adults and children with inhibitors, from Ministry of Health and Social Security Health Insurance, comparing current scheme with emicizumab prophylaxis.

Institution, type of patient, and management scheme	PV of medical costs per patient (US$)	PV of incremental medical costs per patient (US$)	PV of efficiency (QALYs)	PV of incremental effectiveness (QALYs)	Cost-effectiveness ratio (US$ / QALY)	Number of annual bleedings
Ministry of Health						
Adultos	19 481 077	N/A	24.22	N/A	N/A	2
Emic + s/ITI + TxFE/F7	31 278 254	-11 797 177	23.66	0.56	-21 032 639	8
ProFE + ITI + TxFE/F7						
Children without ITI	4 879 610	N/A	12.87	N/A	N/A	1
Emic + ITI + TxFE/F7	19 910 776	-15 031 166	12.52	0.36	-42 127 646	8
ProFE + ITI + TxFE/F7						
Children with ITI	7 513 142	N/A	12.87	N/A	N/A	1
Emic + ITI + TxFE/F7	22 183 281	-14 670 139	12.52	0.36	-41 115 799	8
ProFE + ITI + TxFE/F7						
Social Security Health Insurance						
Adults	19 481 077	N/A	24.22	N/A	N/A	2
Emic + s/ITI + TxFE/F7	59 545 139	-40 064 062	23.86	0.36	-110 183 957	6
ProFE + ITI + TxFE/F7						
Children without ITI	4 879 610	N/A	12.87	N/A	N/A	1
Emic + ITI + TxFE/F7	17 631 320	-12 751 710	12.62	0.25	-50 496 889	6
ProFE + ITI + TxFE/F7						
Children with ITI*						
Emic + ITI + TxFE/F7	7 513 142	N/A	12.87	N/A	N/A	1
ProFE + ITI + TxFE/F7	22 382 632	-14 869 490	12.62	0.25	-58 883 315	6

PV: present value; Emic: prophylaxis with emicizumab; ITI: with immunotolerance; ProFE: prophylaxis with an anti-inhibitor coagulant complex; s/ITI: without immunotolerance; TxFE/F7: treatment of bleeding with anti-inhibitor coagulant complex or recombinant activated factor VII; s/Pro: without prophylaxis; N/A: not applicable.
[1]ITI during 9 months.
Source: Prepared by the authors of this study.

Social Security Health Insurance since it increases effectiveness and reduces costs.

A univariate sensitivity analysis was performed, showing the results obtained by modifying each parameter between a minimum and a maximum value. This analysis showed that despite the patient's age and the current type of treatment, the adoption of emicizumab generates savings and improvement in health status (Table 7).

A probabilistic sensitivity analysis was also performed (Figure 3). The results are presented graphically below for children. This analysis shows that in almost 100% of the simulations, emicizumab prophylaxis would be cost-effective compared to the other treatments, with a threshold of less than US$ 45 258.

The budget impact would be favorable for public finances. The adoption of emicizumab prophylaxis would result in significant net savings for the Ministry of Health and the Social Security Health Insurance (Table 8), producing an annual net savings of US$12.8 million in the former. In present value over five years, the savings would be US$ 58.8 million. In the Social Security Health Insurance, emicizumab prophylaxis would also result in considerable net savings: These would be US$ 15.0 million per

Table 7. Sensitivity analysis from Ministry of Health and Social Security Health Insurance: Minimum, base, and maximum values per variable, maximum and minimum results, and their difference for the Incremental Cost-Effectiveness Analysis (ICER) per variable (US$).

	Variable values			ICER results		
Variable	**Minimum**	**Base**	**Maximum**	**Minimum**	**Maximum**	**Difference**
Ministry of Health						
Adults						
Percentage of patients with mild bleeds	0.85	0.90	0.95	-25 596 339	-17 061 728	8 534 611
Q of annual anti-inhibitor coagulant complex bleeds	7	8	9	-23 814 930	-17 062 880	6 752 050
Q of annual Emic bleeds	1	2	3	-22 923 217	-18 176 176	4 747 041
Emic costs	6256	7820	N/A	-25 190 793	-21 032 639	4 158 154
Mild bleeding costs*	159 801	159 847	N/A	-21 032 639	-21 020 752	11 887
Severe bleeding costs*	160 011	162 529	N/A	-21 032 639	-21 024 606	8 033
Children with inhibitors without ITI						
Q of annual Emic bleeds	0	1	2	-46 385 902	-39 100 667	7 285 235
Percentage of patients with mild bleeds	0.85	0.90	0.95	-45 974 401	-38 781 574	7 192 827
Q of annual anti-inhibitor coagulant complex bleeds	7	8	9	-45 596 139	-39 543 589	6 052 550
Emic costs	3511	4389	4 389	-44 108 235	-42 127 646	1 980 589
Mild bleeding costs*	104 138	104 184	104 184	-42 127 646	-42 116 123	11 522
Severe bleeding costs*	104 348	106 866	106 866	-42 127 646	-42 119 859	7 787
Children with inhibitors with ITI						
Q of annual Emic bleeds	0	1	2	-45 342 211	-38 111 458	7 230 753
Percentage of patients with mild bleeds	0.85	0.90	0.95	-44 937 418	-37 793 675	7 143 744
Q of annual anti-inhibitor coagulant complex bleeds	7	8	9	-44 580 419	-38 534 629	6 045 790
Emic costs	6783	7661	N/A	-43 096 389	-41 115 799	1 980 589
Mild bleeding costs*	104 138	104 184	N/A	-41 115 799	-41 104 277	11 522
Severe bleeding costs*	104 348	106 866	N/A	-41 115 799	-41 108 013	7 787
Social Security Health Insurance						
Adults						
Q of annual Emic bleeds	1	2	3	-145 850 908	-91 557 942	54 292 966
Q of annual anti-inhibitor coagulant complex bleeds	5	6	7	-139 408 841	-93 432 103	45 976 738
Percentage of patients with mild bleeds	0.85	0.90	0.95	-114 095 694	-106 766 397	7 329 298
Emic costs	6256	7820	N/A	-116 598 243	-110 183 957	6 414 286
Mild bleeding costs*	159 801	159 847	N/A	-110 183 957	-110 171 733	12 224
Severe bleeding costs*	160 011	162 529	N/A	-110 183 957	-110 175 696	8 261
Children with inhibitors without ITI						
Q of annual Emic bleeds	0	1	2	-59 690 709	-44 847 602	14 843 107
Q of annual anti-inhibitor coagulant complex bleeds	5	6	7	-57 947 856	-45 596 139	12 351 718
Percentage of patients with mild bleeds	0.85	0.90	0.95	-54 332 693	-47 133 300	7 199 393
Emic costs	3511	4389	N/A	-53 295 329	-50 496 889	2 798 441
Mild bleeding costs*	104 138	104 184	N/A	-50 496 889	-50 485 260	11 629
Severe bleeding costs*	104 348	106 866	N/A	-50 496 889	-50 489 030	7 859
Children with inhibitors with ITI						
Q of annual Emic bleeds	0	1	2	-70 976 396	-51 452 532	19 523 864
Q of annual anti-inhibitor coagulant complex bleeds	5	6	7	-69 031 075	-52 208 794	16 822 281
Percentage of patients with mild bleeds	0.85	0.90	0.95	-62 888 917	-55 356 536	7 532 380
Emic costs	6783	7661	N/A	-61 681 755	-58 883 315	2 798 441
Mild bleeding costs*	104 138	104 184	N/A	-58 883 315	-58 871 686	11 629
Severe bleeding costs*	104 348	106 866	N/A	-58 883 315	-58 875 456	7 859

(Cont.)

Table 7. Cont.

	Variable values	ICER results

ICER: Incremental Cost-Effectiveness Analysis; Q: quantity; ITI: with immunotolerance; Emic: emicizumab; N/A:: not applicable.
[1]includes pharmacological costs and other health benefitis.
Source: Prepared by the authors of this study.

year. Over five years, the present value of these savings would be US$ 68.7 million at the list price of emicizumab. In an alternative scenario – in which the price of emicizumab had a 20% discount (a possibility raised by Roche to the authors) – in five years, the savings for the Ministry of Health would be US$ 62.0 million and US$ 72.3 million for the Social Security Health Insurance.

At the time of writing, the Ministry of Health uses donations to finance treatment of bleeds in hemophilia patients. In addition, some patients may also have to make payments or co-payments, the magnitude of which is not documented. Our budget impact analysis assumes that the Ministry of Health currently funds the drugs from its resources. However, if the funding comes in part from donations and patient payments, the budget impact of adopting emicizumab would be less (by an unknown amount) than what we estimate, at least for the Ministry of Health.

DISCUSSION

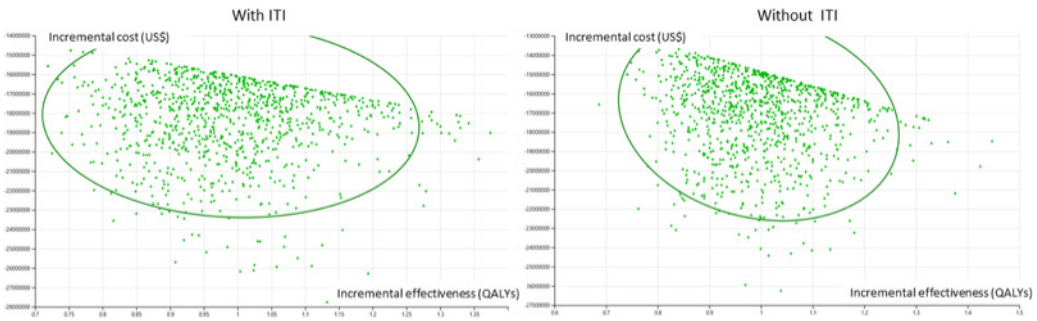
The management of severe hemophilia A by treating bleeds "on-demand" generates enormous healthcare costs, causes severe disability in patients, and reduces their life expectancy. On the other hand, prophylaxis with an anti-inhibitor coagulant complex with and without immunotolerance is also very expensive. Similarly, its results on patient health are not as good as those obtained when prophylaxis is performed with emicizumab. The results of this study show that the two large public health institutions in Peru – which provide medical care to almost the entire population of the country – currently incur high costs in managing severe hemophilia A, while their patients unnecessarily experience a high burden of disease. They also show that emicizumab prophylaxis would generate considerable economic savings for these two institutions and improve the health status of severe hemophilia A patients. These results are consistent with other studies published in developed countries, as shown in Table 1.

The methodology adopted in this work, with the formulation of a Markov model that accounts for the life cycle of patients with severe hemophilia A and the different health states through which they pass, is consistent with other studies in this field, including the most recent one conducted by the Institute for Clinical and Economic Review. Moreover, this effort brought together some of Peru's leading hemophilia experts to document (for the first time) the costs of managing severe hemophilia A through the Ministry of Health and the Social Security Health Insurance. These experts also contributed to estimating the gains in health status and medical expenditure that would result from emicizumab as prophylaxis for severe hemophilia A.

One of the uncertainties of this work stems from the lack of knowledge of the actual costs of healthcare in the Ministry of Health and Social Security Health Insurance hospitals. Using the costs of a private clinic as a proxy could overestimate the actual costs of these two institutions in managing hemophilia. However, simulations of healthcare costs show that even if public costs were substantially lower than private costs, the study's main result would not change.

We should note that it is uncommon to obtain as a result of a cost-effectiveness study that new medical technology will reduce costs and improve the health status of patients. It is usual that for the burden of disease produced by a given pathology, the health system should incur a higher cost than current management. The fact that emicizumab prophylaxis is dominant speaks to the high convenience of adopting this treatment strategy.

Figure 3. Results of probabilistic sensitivity analysis: incremental cost-effectiveness plan.



Source: Prepared by the authors of this study.

Table 8. Budget impact from the Ministry of Health and and the Social Security Health Insurance (US$), in adults and children, comparing current scheme with emicizumab prophylaxis (US$).

Institution, type of patient, management scheme, and price discount for emicizumab	Number of patients	PV of incremental medical costs per patient	Weekly cycle cost	PV of incremental medical costs per patient in one week	Annual savings per patient in one year	Annual savings for all patients in one year	PV to 5 years
Ministry of Health							
Scenario without discount							
Children (<18 years old)	8	-14 670 139	830	22 248	1 156 900	9 255 202	
Adults (>18 years old)	8	-11 797 177	2707	8 614	447 919	3 583 350	
Total	16					12 838 552	58 796 811
Social Security Health Insurance							
Scenario without discount							
Children (<18 years old)	5	-14 869 490	830	22 550	1 172 621	5 863 106	
Adults (>18 years old)	6	-40 064 062	2707	29 253	1 521 164	9 126 986	
Total	11					14 990 092	68 650 233

PV: present value.
Source: Prepared by the authors of this study.

Conclusion

This analysis has shown that emicizumab as prophylaxis for severe hemophilia A in children and adults covered by the Ministry of Health or the Social Security Health Insurance is a dominant cost-effective strategy: it provides better health outcomes at lower costs than the current therapeutic scheme. Its use would generate considerable improvements in the health status of all child and adult patients with severe hemophilia A. In addition, it would produce five-year net savings for the Ministry of Health and the Social Security Health Insurance of US$ 58.8 million and US$ 68.7 million, respectively, considering the current number of patients. These savings and benefits are maintained by performing sensibility analysis in any model variable.

The resources saved from using emicizumab as prophylaxis for severe hemophilia A could be allocated to the prevention or treatment of other diseases.

Given the above, it is highly advisable that the public health system in Peru – including the Ministry of Health and the Social Health Insurance – implement protocols for the prophylaxis and treatment of hemophilia and fund emicizumab directly from their budget.

Notes

Contributor roles

RB: principal investigator, data collection, methodology, validation, visualization, original draft writing, revision writing, and editing. CP: literature review, data collection, methodology. PA: data collection, methodology, validation, visualization. NL, KS, CV, GC, VS: data collection, validation.

Competing interests

The authors have completed the ICMJE conflict of interest declaration form and declare receiving funding from Roche Peru for this work. The forms can be requested by contacting the corresponding author or the Editorial Direction of the Journal.

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Ethics

Given the attributes of the study (open access secondary data), no ethics committee was required.

Provenance and peer review

Not commissioned. Externally peer-reviewed by three reviewers, double-blind.

Language of submission

Spanish.

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Estudio de costo-efectividad de profilaxis con emicizumab versus agentes hemostáticos alternativos en pacientes con hemofilia A grave en Perú

Resumen

Contexto

La hemofilia es un trastorno hemorrágico de la coagulación que ocurre en uno de cada 5000 nacimientos masculinos. Los pacientes con hemofilia A grave no tratados tienen complicaciones hemorrágicas, incluyendo sangrados articulares y menor sobrevida. El emicizumab es un anticuerpo monoclonal aprobado por los Estados Unidos para la profilaxis rutinaria de pacientes pediátricos y adultos con hemofilia A grave con inhibidores del factor VIII de coagulación.

Objetivos

Realizar un estudio de costo-efectividad de la profilaxis con emicizumab para niños y adultos con hemofilia A grave, en comparación con el actual manejo de esos pacientes en el Ministerio de Salud y el Seguro Social de Salud de Perú.

Metodología

Se modeló la transición del paciente entre estados médicos con la metodología de Markov y se estimó a lo largo de su vida costos y efectos incrementales de emicizumab comparados con el actual manejo. Se estimó el impacto presupuestario de emicizumab proyectando costos netos anuales y su valor presente a cinco años.

Resultados

Emicizumab generaría ahorros en el Ministerio de Salud entre 14,6 y 16,0 por niño y 11,8 por adulto, en US$ millones actuales, y en el Seguro Social de Salud de 12,8 a 14,9 por niño y 40,1 por adulto. Además, se generan ganancias en efectividad, medidas en años de vida ajustados por calidad, de 0,36 por niño y 0,56 por adulto y de 0,25 por niño y 0,36 por adulto en esas respectivas instituciones. El impacto presupuestario sería un ahorro anual neto, en US$ millones, de 12,8 y 15,0 en esas entidades.

Conclusión

El actual manejo de la enfermedad es muy costoso y con resultados de salud inferiores a los posibles con emicizumab. Este fármaco produciría grandes ahorros y mejor salud. Ambas entidades debieran implementar protocolos para la profilaxis y tratamiento de la hemofilia y financiarla con presupuesto propio.