Economic evaluation of immune tolerance induction for children with severe hemophilia A and high-responding inhibitors: A cost-effectiveness analysis of prophylaxis with emicizumab

RUNNING TITLE: Cost-effectiveness of emicizumab on ITI

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ABSTRACT

Introduction: The development of anti-factor VIII (FVIII) neutralizing antibodies (inhibitors) increases the morbidity and mortality of people with severe hemophilia A (PsHA). Immune tolerance induction (ITI) is the treatment of choice to eradicate inhibitors. Due to the bleeding risk, PsHA and high-responding inhibitors (PsHAhri) on ITI require prophylaxis with bypassing agents (BpA). Recently, the effectiveness of prophylaxis with emicizumab, a bispecific antibody which mimics FVIII, has been under investigation. Aim: To measure the cost-effectiveness of prophylaxis with emicizumab in PsHAhri on ITI in Brazil. Methods: A cost-effectiveness modelling analysis was used to estimate the costs per PsHAhri on ITI and the number of prevented bleedings from undertaking one intervention (prophylaxis with BpA) over another (prophylaxis with emicizumab), based on the Brazilian Ministry of Health perspective. Costs of ITI with recombinant FVIII, prophylaxis with BpA or emicizumab, and treated bleeding episodes with BpA costs were evaluated for PsHAhri who had ITI success or failure. This study was conducted with the perspective of the Brazilian Ministry of Health (payer). Results: During ITI, prophylaxis with BpA cost US$924,666/PsHAhri/ITI, while prophylaxis with emicizumab cost US$488,785/PsHAhri/ITI. During ITI, there was an average of 9.32 bleeding episodes/PsHAhri/ITI when BpA was used as prophylaxis and 0.67 bleeding/PsHAhri/ITI when emicizumab was used. By univariate deterministic sensitivity analysis, emicizumab remained dominant whichever variable was modified. Conclusion: In this study, prophylaxis with emicizumab during ITI is a dominant option compared with prophylaxis with BpA during ITI.

Keywords: cost-effectiveness analysis; immune tolerance induction; prophylaxis; emicizumab; bypassing agents; recombinant activated factor VII; activated prothrombin complex concentrate.

HIGHLIGHTS:

- The development of anti-factor VIII antibodies (inhibitor) is related to worse outcomes of treatment of people with severe hemophilia A (PsHA).
- Immune tolerance induction (ITI) is the treatment of choice to eradicate inhibitors in PsHA and high-responding inhibitors (PsHAhri). The effectiveness of bypassing agents (BpA) for preventing bleeding during ITI is already known. Assuming the same effectiveness of emicizumab in preventing bleeding in PsHAhri not under ITI, we evaluated the cost-effectiveness of emicizumab for PsHAhri undergoing ITI according to the Brazilian ITI Protocol.
- By univariate deterministic and probabilistic sensitivity analyses, emicizumab remained dominant whichever variable was modified.

1) Introduction

Hemophilia A (HA) is a rare X-linked inherited bleeding disorder due to mutations in the coding gene (*F8*), which results in reduced or complete absence of the factor VIII (FVIII) clotting activity.[1] Spontaneous bleedings, mainly hemarthroses and muscle bleeds, are frequent in people with severe HA (PsHA), due to a very low plasma activity of FVIII (less than 1% of the normal).[1] Bleeding after minor traumas and during surgery may also occur.[1] These events may lead to serious impairments and even be fatal.[1] Exogenous FVIII

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intravenous infusion are required to both treat (episodic treatment) and prevent (prophylactic treatment) bleeding.[2] Plasma-derived or recombinant (rFVIII) concentrates are known to be effective and safe.[2] However, the development of anti-FVIII neutralizing alloantibodies (inhibitors) may occur in approximately 30% of PsHA during the first 50 exposition days.[3–5] Inhibitors limit the hemostatic activity of FVIII, rendering the PsHA with a greater risk of bleeding, despite FVIII replacement.[4] This may be more serious among PsHA and high-responding inhibitors (PsHAhri; inhibitor titer of 5 BU/mL or more at least once in a lifetime) because higher doses of FVIII are less effective against high inhibitor activities.[4] Ultimately, the morbidity and mortality risks of PsHAhri are higher than their non-inhibitor counterparts.[4] Consequently, medicines that avoid the need for FVIII are required to adequately treat PsHAhri.[2,4] By-passing agents (BpA), e.g., activated prothrombin complex concentrate (aPCC) or recombinant activated factor VII (rFVIIa), may be prescribed as episodic or prophylactic treatments.[2,4] They have similar effectiveness in both indications.[4] aPCC is a plasma-derived mixture of the vitamin K-dependent factors II, VII, IX, and X, and its main mechanism is to burst the propagation phase of the coagulation process.[6] rFVIIa acts in the initiation phase, directly increasing the factor X activation.[7] The bispecific antibody emicizumab mimics FVIII activity, and is indicated as prophylactic treatment for PsHAhri.[8] Nevertheless, since this molecule has no homology to the FVIII protein structure, anti-FVIII inhibitors do not neutralize its effect.[8]

Despite these treatments, the state-of-the-art treatment for PsHAhri is to eradicate the inhibitor.[2] This is called immune tolerance induction (ITI) and current success rates range from 60% to 90% in up to 37 months of therapy, according to several registries published worldwide.[3,4] ITI consists of regular infusions of FVIII to promote re-tolerance.[2,3] Infusions may be every other day to twice daily.[2,3] Besides that, the bleeding risk during this period may increase, justifying prophylaxis with BpA or emicizumab.[2] BpA have documented effectiveness in such recommendations,[9] but emicizumab is still under research with a significant promise of being successful in preventing bleeding events on ITI.[10–12] However, if a bleeding event during ITI occurs, the episodic treatment must be with BpA.[2] While BpA have a very low risk of thrombosis when individually used,[13] their association (mainly aPCC) with emicizumab is not free of risk.[14,15] The revision of the BpA treatment recommendations for PsHA on emicizumab have greatly reduced the incidence of thrombosis.[2,14,15]
In Brazil, the treatment of HA is guaranteed by the Public Health System (in Portuguese, *Sistema Único de Saúde* [SUS]).[16,17] Since 2011, the Brazilian ITI Protocol was implemented with the aim of providing a treatment option for PsHAhri. In 2019, emicizumab was incorporated into the SUS for the treatment of those who failed ITI.[16,17] According to the Brazilian Immune Tolerance (BrazIT) Study, which aims to register the factors related to the outcome of the Brazilian ITI Protocol, the success rate is about 65%,[18] which means that the remaining 35% PsHAhri who failed ITI will be offered emicizumab as prophylaxis. However, emicizumab is not currently indicated by the Brazilian Ministry of Health as prophylaxis during ITI.

Evaluating the costs of the treatment of HA is complex because the results depend on the type of treatment (episodic, prophylaxis, and/or ITI), the products under evaluation, intensity of dose regimen (low- or high-doses), and bleeding rates. Overall, the costs of the treatment of HA are high. FVIII replacement therapy of one PsHA without inhibitor may cost from €50,000 to more than €200,000 per patient per year (approximately US$62,500 to more than US$250,000, as purchasing power parity [PPP] dollar-to-euro by 2020 being US$1.00 equal to €0.80).[19,20] After developing high-responding inhibitor, the costs of treatment increase twice or more mainly due to BpA treatment.[19,20] ITI costs can be similar to prophylaxis with FVIII but can reach very high levels when a high-dose FVIII regimen is associated with BpA prophylaxis and episodic treatments with BpA.[19,20] In a non-ITI setting, pharmacoeconomic models have recently shown that prophylaxis with emicizumab for PsHAhri is more cost-effective than prophylaxis with BpA.[21–23] However, we believe there has been no study to date that has evaluated the cost-effectiveness of the association between ITI with prophylaxis with emicizumab. Since there is a growing concern regarding ITI for PsHAhri with respect to its costs and effectiveness, there is an urgent need to estimate the impact of introducing emicizumab as a prophylactic agent during ITI. Therefore, the aim of this study was to examine the cost-effectiveness of emicizumab for PsHAhri undergoing ITI according to the Brazilian Immune Tolerance Protocol. Subsequently, we will use the findings to offer guidance to the authorities in Brazil.

2. Methods

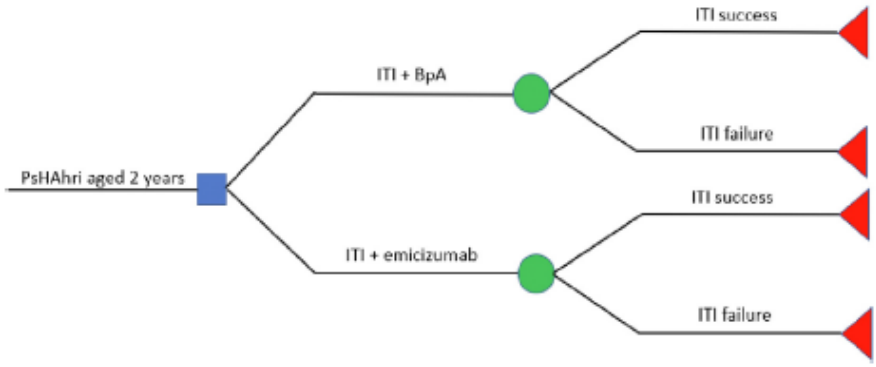
2.1 Model design

We conducted a cost-effectiveness analysis using the TreeAge Pro, LLC software (Williamstown, Massachusetts, United States). A decision tree model was developed to compare the costs and effectiveness of prophylaxis with BpA (aPCC or rFVIIa) or emicizumab in preventing bleeding events during the ITI period in PsHAhri, with the perspective of the Brazilian Ministry of Health (payer; Figure 1). Episodic treatment with BpA was not evaluated since the current recommendation of treatment of PsHAhri with a bleeding phenotype is prophylaxis.[2]

The target population for this analysis were male PsHAhri aged 2 years undergoing ITI according to the Brazilian ITI Protocol.[24] This age was chosen based on a prospective study of previously untreated people with hemophilia A receiving rFVIII (Advate, α-rurioctocog; Takeda Pharmaceuticals U.S.A., Inc., Lexington, Massachusetts, United States) as prophylaxis in Brazil.[5] According to this study, the median age to develop inhibitor was 15.5 months (interquartile range, 12.0-20.8). As such, we assumed 24 months (i.e., 2 years) as the adequate age to start ITI.

The Brazilian ITI Protocol consists of initiating intravenous infusions of rFVIII at a low-dose regimen (50 IU/kg, 3 times per week). After 6 months, the ongoing response is measured by inhibitor titer decreases bimonthly. If no response is achieved, the regimen is increased up to 100 IU/kg/day. To prevent bleeding events, prophylaxis with BpA (ITI + BpA, Figure 1) is recommended.[24] Both aPCC (FEIBA; Takeda Pharmaceuticals U.S.A., Inc., Lexington, Massachusetts, United States) and rFVIIa (NovoSeven; NovoNordisk A/S, Gentofte, Denmark) are effective as prophylaxis during ITI, apparently without effect on the ITI outcome.[9] The Brazilian ITI protocol recommends prophylaxis with aPCC as 75 U/kg every other day or rFVIIa as 90 µg/kg daily.[24] Emicizumab (Roche, Hertfordshire, Alabama, United States) has recently been studied as for prophylaxis during ITI (ITI + emicizumab, Figure 1).[10–12] However, it is still too early to know its impact on ITI outcome. Emicizumab prophylaxis must start with a loading dose of 3.0 mg/kg once weekly for 4 weeks, followed by a maintenance regimen of 1.5 mg/kg weekly, 3.0 mg/kg every two weeks, or 6.0 mg/kg monthly.[25]

Figure 1. Decision tree model.



BpA indicates bypassing agents; ITI, immune tolerance induction; PsHAhri, people with severe hemophilia A and high-responding inhibitors.

To treat breakthrough bleeds, both PsHAhri on BpA prophylaxis and emicizumab prophylaxis require episodic BpA.[24] Generally, for those PsHAhri on prophylaxis with BpA, the hemostatic factor used to treat bleedings is the same as the patient is receiving for prophylaxis, i.e., aPCC for those on prophylaxis with aPCC and rFVIIa for those on prophylaxis with rFVIIa. However, the association of aPCC and emicizumab is associated with an increased risk of thrombotic events.[2,14,15] Consequently, the first choice to treat bleeding episodes of PsHAhri on emicizumab is rFVIIa.[26] The recommended doses to treat breakthrough bleed in PsHAhri are 75-100 U/kg once or twice daily for aPCC and 90-120 µg/kg every 2-3 h, until the bleeding resolves.[27]

According to the Brazilian ITI Protocol, the maximum treatment period is 33 months,[24] although it can last longer according to individual evaluation. Two outcomes can be reached: success is considered if the PsHA re-tolerates FVIII, while failure means permanent high titers of anti-FVIII inhibitor without hemostatic effect with exogenous FVIII.[24] The data of PsHAhri aged less than 12 years under ITI with rFVIII and prophylaxis with BpA to design the following model inputs were kindly provided by the authors of the BrazIT Study.[28]

2.2 Model inputs

2.2.1 Costs

Since the clotting factors (rFVIII and BpA) and the emicizumab costs correspond to more than 95% of the total costs of HA treatment,[19] only costs associated with the acquisition of these products are being considered. This is because, as mentioned, we evaluated the costs according to the payer perspective (SUS), since the Brazilian Ministry of Health is responsible to both purchasing and distributing medicines throughout the country by this universal healthcare system (Table 1).[29,30] The total cost per PsHAhri was calculated based on the entire ITI period (time horizon), depending on the ITI outcome: 1.8 years in the success group and 3.1

years in the failure group.[28] All costs were converted to US dollar (US$) adjusted by PPP for the 2020 calendar year.[31] According to this currency, the exchange rate is 1 PPP US$ = R$ (Brazilian Real) 2.36.

Table 1. Cost of clotting factors and emicizumab*.

Products	Price – public purchase, 2021[a]	Minimum – according to the recommendation report by CONITEC, 2021[b]	Maximum – according to the suggested values by CMED, 2021[c]
aPCC	1.36/U	0.89/U	1.46/U
rFVIIa	1.20/µg	0.83/µg	1.30/µg
Emicizumab	97.27/mg	69.06/mg	156.59/mg
rFVIII	0.58/UI	--	--

* Exchange rate: 1 PPP US$ = R$ 2.36 (2020)
aPCC, partially activated prothrombin complex concentrate; CMED, Câmara de Regulação do Mercado de Medicamentos (Medicines Market Regulation Chamber); CONITEC, Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde (National Commission for the Incorporation of Technologies in the Unified Health System); PPP, power parity purchase; rFVIIa, recombinant activated factor VII; rFVIII, recombinant factor VIII
[a]https://www.in.gov.br/servicos/diario-oficial-da-uniao;
[b]http://conitec.gov.br/images/Consultas/Relatorios/2019/Relatrio_EMICIZUMABE_HEMOFILIA_A_CP_58.pdf;
[c]https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/cmed

The analysis included ITI costs with rFVIII, prophylaxis costs with both BpA or emicizumab, and episodic costs with BpA (Table 2). Except for prophylaxis with emicizumab, the regimens were extracted from the Brazilian ITI Protocol.[24] For each treatment modality (ITI, prophylaxis, and episodic) the costs were estimated by multiplying the price per unit of the product by the PsHAhri's body weight according to the regimen, and the period of treatment of each ITI outcome (e.g., success or failure). For ITI with rFVIII, we assumed both low- (50 IU/kg, 3 times per week) and high-dose (100 IU/kg/day) regimens, upon unresponsiveness to ITI.[24]

Table 2. Parameters used in the economic model for people with severe hemophilia A and high-responding inhibitors under prophylaxis, according to the respective period of immune tolerance outcome.

Parameters	ITI success	ITI failure	Source
Patient characteristics			
Age at ITI start, in years	2	2	Assumption
Average patient weight, in kg (range)	15.0 (12.0 – 18.0)	16.0 (12.8 – 19.2)	IBGE[34]
ITI characteristics			
ITI regimen (at start), in IU/kg/week			Brazilian ITI Protocol[24]
Low-dose rFVIII	150	150	
High-dose rFVIII	700	700	
Switch from low-dose to high-dose regimens (%)*	14.0%	74.0%	BrazIT Study[28]
Duration of ITI			
In years (IQR)	1.8 (1.3 – 2.6)	3.1 (2.7 – 3.4)	BrazIT Study[28]
In weeks (IQR)	94 (68 – 135)	161 (140 – 177)	BrazIT Study[28]
Maximum (months)	37	37	Assumption
ITI outcome rate (%)	67.7% (success)	32.3% (failure)	BrazIT Study[28]
Prophylaxis characteristics			
Prophylaxis with BpA			
aPCC, in U/kg/week (range)	50% 243.75 (162.5 – 700)	50% 243.75 (162.5 – 700)	Assumption Brazilian ITI Protocol[24], Lopez-Fernandez 2016[9]
rFVIIa, in µg/kg/week (range)	50% 630 (292.5 – 1,890)	50% 630 (292.5 – 1,890)	Assumption Brazilian ITI Protocol[24],

Prophylaxis with emicizumab, in mg/kg/year	84 (first year) 78 (next years)	84 (first year) 78 (next years)	Lopez-Fernandez 2016[9] HAVEN 2[32]
Bleeding episodes characteristics			
Total bleeds during ITI			
PsHAhri under prophylaxis with BpA	5.04 (3.06 – 8.46)	18.29 (8.06 – 33.17)	BrazIT Study[28]
PsHAhri under prophylaxis with emicizumab	0.54 (0.18 – 1.80)	0.93 (0.31 – 3.10)	HAVEN 2[32]
Treatment of bleeding			
PsHAhri under prophylaxis with aPCC: aPCC as hemostatic agent, in U/kg/bleeding (range)	87.5 (50 – 100)	87.5 (50 – 100)	Brazilian Guidance of Hemophilia Treatment[27], Astermark 2007[33]
PsHAhri under prophylaxis with rFVIIa: rFVIIa as hemostatic agent, in µg/kg/bleeding (range)	180 (90 – 270)	180 (90 – 270)	Brazilian Guidance of Hemophilia Treatment[27], Astermark 2007[33]
PsHAhri under prophylaxis with emicizumab: rFVIIa as hemostatic agent, in µg/kg/bleeding (range)	180 (90 – 240)	180 (90 – 240)	Linari 2020[26]

aPCC, partially activated prothrombin complex concentrate; IQR, interquartile range; ITI, immune tolerance induction; PsHAhri, people with severe hemophilia A and high-responding inhibitor; rFVIIa, recombinant activated factor VII; rFVIII, recombinant factor VIII; * PsHAhri who changed the scheduled from low-dose to high dose regimen, stayed 50% of time under low-dose regimen ** Consider the proportion of PsHAhri who switched to high-dose regimens.

We considered that 14% of PsAHhri in the successful ITI arm and 74% of PsAHhri in the failure ITI arm needed to change from low- to high-dose regimen.[28] When needed to increase the dosing regimen,[24] we assumed that PsAHhri stayed 50% of the ITI time in low-dose regimen. Prophylaxis with BpA were assumed as following: aPCC 75 U/kg every other day (e.g., 3.25 times per week or 243.75 U/kg/week) or rFVIIa 90 µg/kg/day (e.g., 630 µg/kg/week).[24] When BpA prophylaxis was used, we assumed it was prescribed throughout the ITI period. Prophylaxis with emicizumab consisted of a loading period of 1 month, coincident with the start of ITI, followed by the weekly maintenance regimen.[32] We assumed every PsAHhri initiated emicizumab prophylaxis at the start of ITI. For treating breakthrough bleeding, we assumed the mean recommended doses were required for hemostasis: one infusion of aPCC at 87.5 U/kg or two infusions of rFVIIa at 90 µg/kg/dose.[27,33]

Since our male population entered the model when 2 years-old, and all treatments are based on the body weight (kg), we considered the age-related weight described previously for the Brazilian male population.[34] We assumed there is no difference between the weight of male PsHAhri and male non-hemophilia age-paired individuals on this age range.

2.2.2 Effectiveness

Effectiveness was evaluated by the total number of treated bleeding events per PsHAhri, according to the two different prophylaxes (e.g., BpA or emicizumab), during the respective ITI duration (e.g., success or failure).[35] The number of bleeding events of PsHAhri under ITI and prophylaxis with BpA was extracted from the BrazIT Study.[28] We assumed that the prophylaxes with aPCC and rFVIIa have the same effectiveness,[36] and, therefore, were grouped into a single category, with 50% of patients using the aPCC and 50% using the rFVIIa. The HAVEN 2 study was referenced for prophylaxis with emicizumab.[32] HAVEN 2 was an open-label phase 3 multicenter trial which assessed prophylaxis with emicizumab in children with HA and inhibitors.[32]

The majority of the included individuals was PsHAhri under 12 years-old.[32] Although HAVEN 2 did not include PsHAhri undergoing ITI, we assumed that the bleeding rates were the same, regardless the patient was on ITI or not. Although the duration of ITI is recommended as 33 months,[24] the amount of PsHAhri treated during longer periods is not negligible. Consequently, we assumed the maximum duration of ITI was 37 months. Finally, we assumed the same success rates as for ITI, regardless of the product used for prophylaxis drug (Table 2).

2.2.3 Sensitivity analyses

Deterministic and probabilistic sensitivity analyses were performed to assess uncertainty and to identify which variables most impacted the results obtained in terms of incremental costs (e.g., total cost incurred due to an additional unit of the variable under investigation). In the deterministic sensitivity analysis, parameters included in testing the robustness of the results were the costs of the clotting factors and emicizumab, the drug regimens, and the number of bleeds and their respective treatment. We used the minimum and the maximum values of each variable described in Table 2. The analysis is illustrated using a tornado diagram. In addition, we evaluated the use of only one BpA as prophylactic agent in ITI. The probabilistic sensitivity analysis was performed using the Monte Carlo simulation. For the drug regimens parameters, the triangular distribution was used, for the cost parameters, the gamma distribution, and for the number of bleeds, a normal distribution was used. No discount rate was applied due to the short time horizon.

3. Results

In the cost-effectiveness analysis, ITI with prophylaxis with BpA (aPCC or rFVIIa) cost US$1,270,836, while the ITI with prophylaxis with emicizumab cost US$546,358, generating an additional cost of US$724,478 for ITI with prophylaxis with BpA per PsHAhri-treatment. ITI with prophylaxis with BpA (aPCC or rFVIIa) resulted in an average of 9.32 bleeds per PsHAhri-treatment, while ITI with prophylaxis with emicizumab resulted in an average of 0.67 bleeding per PsHAhri-treatment. Consequently, in the case of ITI with prophylaxis with BpA (aPCC or rFVIIa), there were higher costs and an estimated increased number of bleeding episodes compared with ITI with prophylaxis with emicizumab (Table 3). Similar cost-effectiveness analysis considering only aPCC as the BpA resulted in an incremental cost of US$388,202 per PsHAhri-treatment, when compared to ITI with prophylaxis with emicizumab (Table 4).

Table 3. Cost-effectiveness analysis of immune tolerance induction with prophylaxes with bypassing agents or emicizumab in Brazil.

Treatment	Cost*	Incremental cost*	Bleeding	Incremental bleeding
ITI + BpA	1,270,836		9.32	
ITI + emicizumab	546,358	- 724,478	0.67	8.65

*Total cost (PPP expressed in US$); Exchange rate: 1 PPP US$ = R$ 2.36 (2020); BpA, bypassing agents (partially activated prothrombin complex concentrate or recombinant activated factor VII); ITI, immune tolerance induction; PPP, power parity purchase.

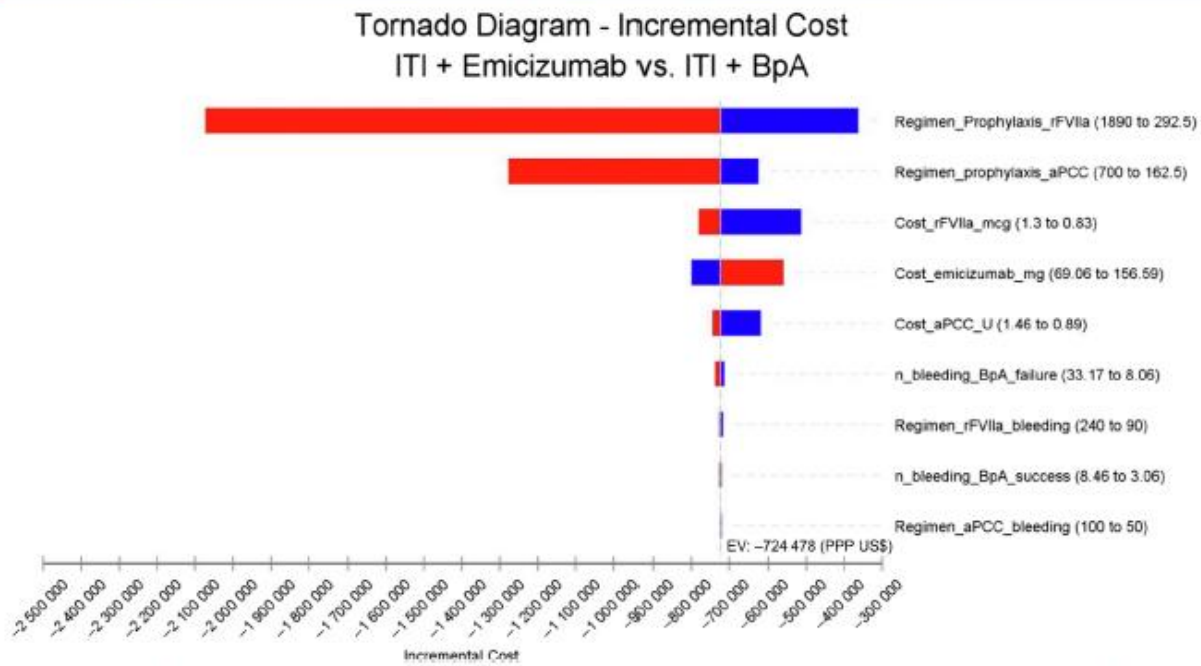
Table 4. Cost-effectiveness analysis of immune tolerance induction with prophylaxes with activated partially activated prothrombin complex concentrate (bypassing agent) or emicizumab in Brazil.

Treatment	Cost*	Incremental cost*	Bleeding	Incremental bleeding
ITI + aPCC	884,560		9.32	
ITI + emicizumab	546,358	- 388,202	0.67	8.65

*Total cost (PPP expressed in US dollars); Exchange rate: 1 PPP dollar = R$ 2.36 (2020); aPCC, partially activated prothrombin complex concentrate; ITI, immune tolerance induction; PPP, power parity purchase.

We performed the deterministic sensitivity analysis to evaluate the variables that could impact the additional cost of ITI with prophylaxis with BpA (aPCC or rFVIIa) in relation to ITI with prophylaxis with emicizumab (Figure 2). The dose regimen of rFVIIa prophylaxis was the variable with the greatest power to change the incremental cost. Even if the dose regimen was reduced is its minimum, the incremental cost of ITI with prophylaxis with BpA (aPCC or rFVIIa) would still be close to US$300,000 above the cost of ITI with prophylaxis with emicizumab. The other variables that impacted the incremental cost of ITI were the dose regimen of prophylaxis with aPCC and the costs of BpA (aPCC or rFVIIa) and emicizumab (Figure 2).

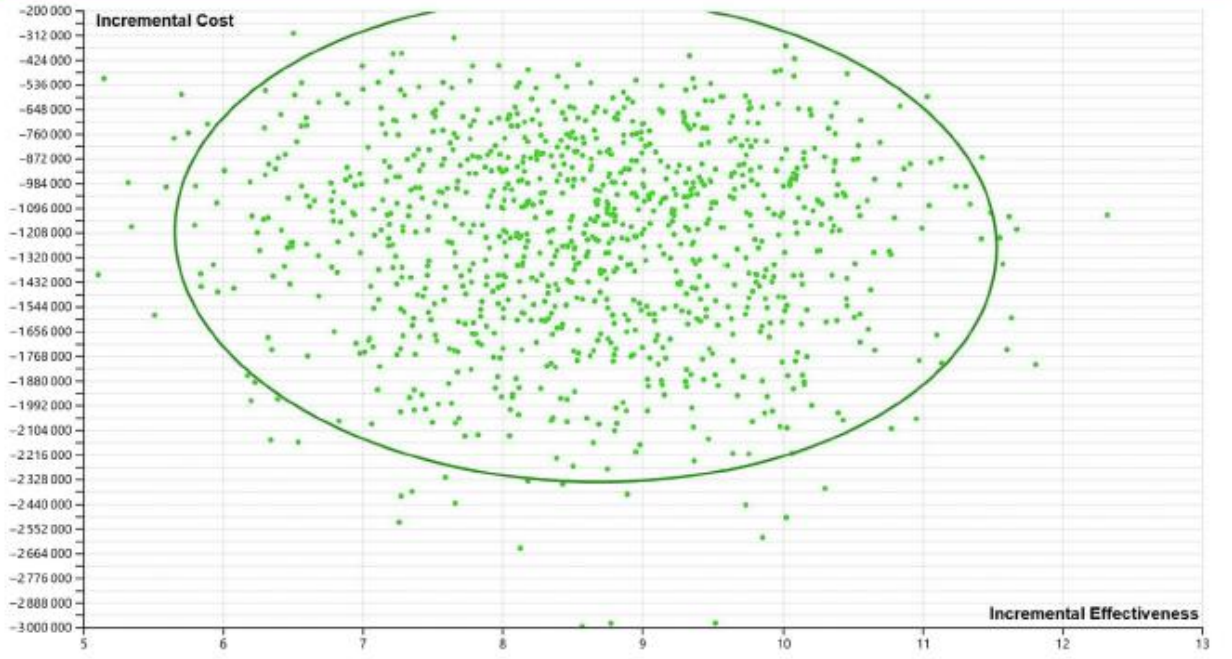
Figure 2. Tornado diagram of one-way deterministic sensitivity. The diagram depicts the variation of incremental cost* from the base-case value of US $724 478, at lower and upper estimate of the value for 9 most influential parameters. The middle of the tornado diagram corresponds to the base-case value, the blue bars represent the cost-effectiveness at a low estimate of each parameter, and the red bars at a high estimate. *PPP expressed in US dollars; exchange rate: 1 PPP dollar = R$ 2.36 (2020).



aPCC indicates partially activated prothrombin complex concentrate; BpA, bypassing agents; EV, estimated value; ITI, immune tolerance induction; PPP, purchasing power parity; rFVIIa, recombinant activated factor VII.

The number of bleeds during ITI with prophylaxes with each BpA and the regimens of bleeding treatments had minimal impact on the incremental cost (Figure 2). In the Monte Carlo probabilistic analysis, with 10,000 repetitions, the probability of prophylaxis with emicizumab during ITI has a lower cost and fewer bleeding events was 100% (Figure 3).

Figure 3. Incremental cost-effectiveness probabilistic sensitivity analysis. The graph depicts the variation of incremental cost (y-axis, in PPP [PPP expressed in US dollars; exchange rate: 1 PPP dollar = R$ 2.36, in 2020]) according to the incremental effectiveness (x-axis, in bleeding events).



PPP indicates purchasing power parity.

3. Discussion

We investigated the cost-effectiveness of ITI with prophylaxis with emicizumab in comparison with ITI with prophylaxis with BpA using a decision tree model. Assuming that bleeding episodes during ITI with prophylaxis with emicizumab were similar to the results described for the non-ITI children evaluated at the HAVEN 2 trial,[32] the use of the combination of ITI (according to the Brazilian ITI Protocol) and prophylaxis with emicizumab was more cost-effective than ITI and prophylaxis with BpA. Moreover, at different scenarios evaluated by a univariate deterministic sensitivity analysis (e.g., BpA regimens, BpA and emicizumab costs, and bleeding events and treatments), ITI associated with prophylaxis with emicizumab was still cost-effective compared with ITI associated with prophylaxis with BpA.

The complexity of ITI costs evaluation involves the regimen and the type of FVIII used for ITI in addition to the occurrence of bleeding events and the related treatments both to prevent and to treat them. Furthermore, the perspective under consideration (e.g., patient or payer) may greatly impact the results. In Brazil, as mentioned, the Ministry of Health is responsible for purchasing and distributing procoagulants for the treatment of HA.[16,17,30] The trading process is responsible for lowering the costs of overall HA treatment.[29,30] However, the cost-effectiveness of different treatment options needs to be evaluated based on real-world data. The first results of the BrazIT Study have recently been reported, which suggests that the ITI treatment carried out in the whole country has similar outcomes to the protocols applied worldwide.[28] However, the introduction of the prophylaxis with emicizumab to prevent bleeding events in PsHAhri is a recent disruptive technology which seems to have been changing the state-of-the-art of HA treatment in many countries.[8] Emicizumab has both a lower price per regimen and a higher effectiveness in preventing bleedings, avoiding the treatment of breakthrough episodes, which result in the cost-savings we found in this model.

ITI remains the treatment of choice of PsHAhri, since the effectiveness of episodic and prophylactic treatments with FVIII (for non-inhibitor PsHA) is better than with BpA (for PsHAhri).[2,3] In addition, after developing a high-responding inhibitor, the costs of the treatment of PsHA doubles due to BpA treatment.[19,20] In France, a retrospective study using administrative healthcare claims database showed that the mean annual costs for HA management (only factors) per patient increased from €173,254 (prophylaxis with FVIII) to €655,612 (prophylaxis with BpA) (from US$216,568 to US$819,515, as PPP dollar-to-euro by 2020 being US$1.00 equal to €0.80).[20] When treating with ITI, the costs reached €735,717 (PPP US$919,646, calculated as mentioned before).[20] An Italian retrospective survey to assess the costs of management of PsHAhri showed that the average annual cost of prophylaxis with FVIII ranged from €180,000 to €200,000 (PPP US$919,646 to PPP US$250,000, calculated as mentioned before), while the average annual cost of prophylaxis with BpA ranged from €750,000, for aPCC, to €830,000, for FVIIa (PPP US$937,500 to PPP US$1,037,500, calculated as mentioned before).[37] ITI annual average costs ranged from €750,000 to €1,000,000 (PPP US$937,500 to PPP US$1,250,00, calculated as mentioned before).[37]

One should argue not performing ITI and keeping the PsHAhri on emicizumab prophylaxis, based on its effectiveness in preventing bleeding events among these individuals.[32,38] However, in the event of a bleeding episode, BpA may be the first-line treatment for hemostasis.[2] This may happen as a spontaneous episode, which seems to be rare,[39,40] but may happen after trauma or during surgery. In the latter cases, bleedings do happen and are frequent, requiring BpA treatment.[41,42] The risk of thrombosis when BpA, mainly aPCC, are associated with emicizumab is well described.[15] Finally, hemostatic effectiveness of FVIII replacement is higher than BpA, and there is no apparent risk with the association of FVIII and emicizumab.[38,43] Based on these statements, eradicating the inhibitors (i.e., ITI) remains the treatment-of-choice for PsHAhri.[2,44]

Whilst the costs of ITI may be extremely high, the lifetime benefits of responding to FVIII justify both the burden of treatment and costs. A decision-analytic model was developed to compare the costs and outcomes of ITI versus prophylaxis and episodic treatment with BpA.[45] The model included success and relapse after the first ITI treatment, the need of a secondary or rescue ITI, the bleeding events, and the mortality.[45] Whilst over the first nine years after starting ITI, this treatment was more costly than the others, the lifetime costs of ITI was lower in comparison with prophylaxis or episodic treatment with BpA.[45] Nevertheless, no study has been performed until now to evaluate the cost impact of using emicizumab as a prophylactic agent during ITI. In a non-ITI setting, pharmacoeconomic models have recently shown that prophylaxis with emicizumab for PsHAhri is associated with reduced costs of treatment of HA compared to prophylaxis with BpA.[21–23] An Australian study evaluated the impact of emicizumab on societal costs, based on changes in the direct and indirect costs incurred by people with moderate or severe HA.[22] The first year of emicizumab reduced annual costs associated with BpA by 92.0%.[22] Compared to prophylaxis with BpA, the overall budget reduction of prophylaxis with emicizumab for people with HA and inhibitors who failed ITI was €45.4 million in a 3-year horizon (PPP US$56.8 million, calculated as mentioned before), according to an Italian study.[21] This same

study showed that prophylaxis with emicizumab was cost-saving, compared to prophylaxis with BpA.[21] Cost reductions ranged from €19,984,465/patient lifetime (compared to prophylaxis with aPCC) to €25,272,190/patient lifetime (compared to prophylaxis with rFVIIa) (PPP US$24,980,581 to PPP US$31,590,238, respectively, calculated as mentioned before).[21] Prophylaxis with emicizumab was always cost-effective despite the variables used in the probabilistic sensitivity analysis.[21] Similar results were reported in a French study, in a 5-year horizon: compared to prophylaxis with BpA, prophylaxis with emicizumab was cost-saving (€234,191/patient in 5 years, or PPP US$292,739, calculated as mentioned before) for a gain of quality-adjusted life years 0.88, confirmed by both deterministic and probabilistic analyses.[23] The later study also considered the adverse events costs and the wastage for emicizumab.[23] The Italian and the French studies used the Markov model to evaluate the cost-effectiveness of the treatments.[21,23]

Our study has some limitations. Firstly, mortality was not included in the analysis. This is because ITI is a fast-moving therapy for an acute clinical condition, without recent reports of associated death. Secondly, due to its short-term duration, we assumed that long-term models (e.g., Markov model) would generate many uncertainties.[46] Thirdly, we assumed that the risk of adverse events with both emicizumab and BpA are too rare based on current protocols, even rarer in this short-term horizon. Fourthly, we are aware that the bleeding rate during ITI may increase, when compared with the period before ITI start. However, data are lacking about how much this increase would be for PsHAhri on ITI under prophylaxis with emicizumab. In addition, the tornado diagram did not show any impact of the amount of bleeding events on the savings of prophylaxis with emicizumab in comparison with prophylaxis with BpA. Lastly, we did not evaluate the wastage for emicizumab.[47] This is despite being aware that the emicizumab vials do not correspond to the maximum calculated amount of the drug to be administered to the patient and wastage may well happen.[47] For the analysis, we only considered the exact amount of emicizumab the patient should receive. We are currently involved with another study to evaluate the wastage and actions to minimize this loss. However, in the meantime, we believe our findings are robust and can provide guidance to health authorities and payers.

4. Conclusion

By adopting the Brazilian Ministry of Health perspective, our model showed that prophylaxis with emicizumab during ITI may be considered dominant (reduced costs and reduced bleeding events) compared with prophylaxis with BpA.

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