Hemofilia A congénita con inhibidores e inducción de inmunotolerancia en niños y adolescentes jóvenes: ¿podría Brasil ser un ejemplo para otros países?

Congenital hemophilia A with inhibitors and immune tolerance induction in children and young adolescents: could Brazil be an example for other countries?

Christiane Maria da Silva Pinto, MD[1]; Liliana Martins da Silva[2]; Fabio Ferreira de Carvalho Jr, MD[2]

[1] *Pediatric Hematology Department, Federal University of São Paulo.*
[2] *Medical Affairs Department, Takeda Pharmaceuticals Brazil.*

christianemsp@gmail.com

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Abstract

Brazil has the third highest population of patients diagnosed with hemophilia A in the world and the first in Latin America. Factor VIII (FVIII) replacement prophylaxis is the standard of care currently recommended worldwide. However, about 30% of all patients with severe hemophilia A will develop neutralizing antibodies against FVIII, called inhibitors. The proposed aim of immune tolerance induction (ITI) therapy is to eradicate inhibitors, and several protocol variations are available. In Brazil, ITI treatment follows an escalating rationale, initiating with a low-dose scheme using FVIII 50 IU/kg, three times a week. When the absence of a decline in inhibitor titer with a low-dose regimen of at least 20%, in every six-month period after the beginning of ITI, is observed, it is recommended to initiate high-dose scheme using FVIII 100 IU/kg every day. About one third of all patients with hemophilia A are children and adolescents. Disease management in this population prompts different challenges, potentially leading to chronic and lifelong disabilities, and the age at first treatment also seems to act as a risk factor for inhibitor development. In this narrative review, the authors' conclusion provides comprehensive knowledge regarding severe congenital hemophilia A with inhibitors (CHAWI) and ITI in children and adolescents, discussing different ITI protocols, with different outcomes, focusing on comparing Brazil's with other global guidelines.

Introduction

Brazil has a large population diagnosed with hemophilia A. Among nations with the highest number of cases, Brazil represents the third country in the world and the highest in Latin America. According

to the World Federation of Hemophilia (WFH), 10,821 patients were living with the condition in the country in 2019, 29% of them aged between 0 and 18 years[1].

The standard of care is factor VIII (FVIII) replacement, currently recommended worldwide[2,3]. However, about 30% of all patients with severe hemophilia A will develop neutralizing antibodies against FVIII, called inhibitors, usually within 20 exposure days[4,5]. According to data reported in a systematic review, an overall inhibitor incidence rate of 2.06 per 1,000 person-years is observed[6]. The response to elevated FVIII doses is observed with low titer, ranging from 0.6 to 5 Bethesda units (BU). Above 5 BU there is no response to FVIII infusion, related to the high titer inhibitor (HTI)[3,7].

The presence of HTI titer >5BU leads to the neutralization of all infused FVIII which renders patients resistant to conventional replacement treatment[7]. Thus, inhibitors are known as the main complication for patients with hemophilia, since they are associated with increased morbidity and economic burden[7,8].

In this context, immune tolerance induction (ITI) therapy with or without bypassing agents is proposed to eradicate inhibitors[9]. ITI was first proposed in the 1970s by Dr Hans-Hermann Brackmann in Bonn (Germany), known as the "Bonn protocol", consisting of high doses of FVIII and activated prothrombin complex concentrates administration twice a day. In the last decades, several protocol variations were proposed[8].

According to the WFH report on the 2019 global survey, the FVIII utilization in Brazil was 4.309 IU/capita, the third highest among upper middle-income countries from the Americas, after Colombia (4.911 IU/capita) and Argentina (4.312 IU/capita) [1]. However, the wider use of FVIII presents some barriers of access, such as its availability and its high costs.

About one-third of all patients with hemophilia A are children and adolescents[1]. Disease management in children prompts different challenges, potentially leading to chronic and lifelong disabilities. Bleeding episodes among pediatric population can cause physical and mental impairment, affecting education and patients' quality of life[10,11]. In addition, the age at first treatment also seems to act as a risk factor for inhibitor development, highlighting the need for discussion of disease management in this group[12]. Considering this rationale, a narrative review was done aiming to provide a comprehensive knowledge regarding severe congenital hemophilia A with inhibitors (CHAWI) and ITI in children and adolescents discussing different ITI protocols, with different outcomes, focusing on comparing Brazil's with other global guidelines.

Inhibitors eradication and the reposition of FVIII

Patients with hemophilia A present with reduced blood levels of FVIII, which precludes the normal coagulation cascade, and are unable to form a stable fibrin network due to FVIII deficiency[13,14]. Thus, FVIII replacement is considered the central pillar of disease management and the standard of care recommended worldwide[2,3,9].

Inhibitor presence may be diagnosed by an abnormal bleeding episode following a FVIII infusion or by periodic screening in the first 50 days of FVIII treatment. The Modified Nijmegen-Bethesda Assay (MNBA) blood clotting test is used to assess the quantitative presence of inhibitor. Antibody titration can be performed using this test and is described as the number of BU[15]. This measure also defines response to inhibitors eradication strategies[16].

In this context, the development of neutralizing antibodies against FVIII, the inhibitors, represents one of the major complications in the setting of hemophilia[8,17]. ITI was first used in the 1970s in Germany and remains the standard of care in several protocols[8]. These treatment strategies vary according to the duration of administration. Proper patient monitoring using the proper criteria for success, partial success and failure, is essential. In fact, these criteria were defined by an international committee to create a global consensus so that the results are comparable[16,18].

Beyond ITI and its high doses of FVIII administration, patients with HTI may also use other coagulation factors to control bleeding[8,19]. Bypassing agents are products that promote hemostasis through mechanisms alternate to the physiological tenase complex, indicated in these cases. In Brazil, currently, there are two preparations available for the use in clinical practice: the activated prothrombin complex concentrates (aPCC) and recombinant activated factor VII (rFVIIa)[20]. These bypassing agents showed efficacy in preventing bleeding events in subjects

with HTI and no differences between agents or an optimum dosage regimen were observed[21].

In Argentina, a study was designed to assess the annualized bleeding rate in patients with hemophilia A with FVIII inhibitors treated throughout 2017 who were receiving on-demand or prophylactic treatment with bypassing agents and ITI therapy in a real-world setting. Considering both adult and pediatric patients, most patients (56.5%) received on-demand treatment, 13 (18.8%) received prophylactic treatment, and 17 (24.6%) received ITI therapy.

Furthermore, prophylactic treatment (incidence rate ratio (IRR) 0.41, 95%CI: 0.21-0.79, p<0.01) and ITI (IRR 0.47, 95% CI: 0.27-0.81, p<0.01) therapy have shown a significant decrease in the annualized bleeding rate when compared with on-demand treatment[22].

Early prophylaxis and central venous access devices' associated complications

A retrospective 10-year review described the experience with implantable venous access device placement (port placement) in children and adolescents with severe hemophilia (<1% of the factors VIII or IX) at The Children's Hospital of Philadelphia. Central line-associated bloodstream infections (7/24; 29.2%) and transition to the peripheral infusion (3/24; 12.5%) were the most common reason for ports removal, which occurred in 14/24 cases. Considering the first 30 days after placement, bleeding was the most common complication. Nine central line-associated bloodstream infections events (0.57 per 1,000 catheter days) among patients with high neutralizing inhibitor titers were reported. Higher infection rates correlated with a higher frequency of port access (p=0.02) and a median time from port insertion to the first infection of 348 days (167-1,055 days) was reported. Port maintenance in boys with severe hemophilia was highlighted as an important challenge on disease management by the authors, given the need for long-term frequent device access associated with catheter-related infections[23].

A Chilean retrospective study reported that none of the patients treated with plasma-derived FVIII concentrate at 70-180 IU/kg/day, who required a central venous catheter, have completed the treatment using this route of administration. Infection occurrence was the reason for line removal among 3 patients[24].

WFH guidelines state that complications and risks associated with surgical implantation of central venous access devices shall be weighted against the advantages of early initiation of intensive prophylaxis. A shift from the use of central venous access devices to peripheral venous access for early initiation of prophylaxis has been proposed by hemophilia treaters. The procedure starts with once-weekly prophylaxis then gradually escalates infusion frequency, together with more intensive caregiver training[9].

How is ITI proposed worldwide?

Several ITI protocols are available worldwide[8]. Table 1 shows different characteristics of such strategies.

The International Immune Tolerance Study was a randomized controlled trial conducted to test the hypothesis that overall response to ITI is independent of FVIII dosing regimen in good-risk subjects. Patients were randomized into two groups: high-dose regimen, 200 IU/Kg/day and low-dose regimen, 50 IU/Kg three times a week. Results showed no difference between groups regarding success proportion (p=0.909), however, patients allocated to low-dose regimen had more bleeding episodes (odds ratio, 2.2; p=0.0019). Furthermore, the times taken to achieve a negative titer (p=0.027), a normal recovery (p=0.002), and tolerance (p=0.116, non-significant) were shorter with the high-dose ITI[18].

A retrospective study reported the experience of pediatric patients who underwent ITI in the Chilean public health care network. Plasma-derived FVIII concentrate was used at 70-180 IU/kg/day doses. Only two patients with hemorrhagic phenotype received prophylaxis with bypassing agents (rFVIIa or aPCC) during the ITI regime. In total, 84.6% (n = 11) of patients recovered the half-life of FVIII after 49.6 months of treatment. The inhibitor titer was negative at 6 months on average in the patients who responded to treatment. The authors suggest that ITI should be the treatment of choice for hemophilia A and inhibitor persistence patients and that the strategy must be personalized since the time response is variable in each patient[24].

WFH guidelines for the management of hemophilia, 2020, suggest ITI for patients with hemophilia A who develop inhibitors. The document highlights that an optimal regimen, which states the best product or dose to be used, still needs to be defined[9]. Guidelines from United States, published in 2015,

recommend high-dose regimen (200 IU/Kg/day) for patients aged <8 years and daily FVIII 100 IU/Kg as an alternative option[25]. Australian guidelines, published in 2016, states that an optimal regimen is not defined; however, suggests a typical regimen of 100 IU/Kg/day with escalating treatment in difficult cases and the use of high-dose regimen for patients with high risk of failure[26].

In order to understand the scenario of ITI recommendation for pediatric population in Latin American countries, excluding Brazil, electronic searches were performed. Figure 1 shows search strategies used in the main literature database. In addition, websites from societies and/or associations involved in disease management and agencies responsible for health administration in each country were also consulted.

Recommendations were found for Argentina, Chile and El Salvador. Detailed information is reported in table 2. All recommendations state that ITI is the ideal management strategy for patients with HTI, however, no details are provided on schemes and dose options[27-30].

A document published by the Chilean Ministry of Health states that there is no consensus about ideal dosage, with protocols recommending doses from 50 IU/kg three times a week to 300 IU/kg every day, but also highlights that high doses seem more effective when the maximum titer is >200 BU and, regardless of the titer, in all cases, higher dose shortens the ITI time[28].

Regarding the response to ITI, Chilean and El Salvadoran documents stratify patients by total, partial, and no response. Total response is defined as the patient with inhibitor titer undetectable (≤0.6 BU) and normal pharmacokinetics[28,29]. Chilean recommendation states normal pharmacokinetics as recovery of >66% of the administered factor and/or

Table 1. Immune tolerance induction protocols available worldwide. Adapted from the protocol for ITI use in patients with hemophilia A and inhibitor, Brazilian Ministry of Health, 2015[41].

Protocol	Doses	Success (%)	Success definition	Mean titer pre-ITI	Mean length (weeks)
Bonn	200-300 IU/Kg/day	73-87	Normal FVIII R/S	8.8 (<10)	15.0
Malmö	FVIII >30% + IM	80	Normal FVIII R/S	<10 (4.5)	1.3
Smith	200 IU/Kg/day	100	Normal FVIII R/S	2.9	5.0
Rocino	100 IU/Kg/day	80	Normal FVIII R/S	3.6	13.0
Kasper	50 IU/Kg/day	73	Normal FVIII R/S	0.7	3.0
Holanda	25 IU/Kg (3x/week)	83	Inhibitor titer <2 BU	2.5	12.0
Gruppo	100 IU/Kg/day + IM	63	Negative inhibitor	2.5	24.0

Figure 1. Search strategy.

Database	Controlled vocabular
Pubmed	("Hemophilia A"[Mesh]) AND ("Child"[Mesh] OR "Adolescent"[Mesh]) AND (Clinical pathway[mh] OR Clinical protocol[mh] OR Consensus[mh] OR Consensus development conferences as topic[mh] OR Critical pathways[mh] OR Guidelines as topic [Mesh:NoExp] OR Practice guidelines as topic[mh] OR Health planning guidelines[mh] OR guideline[pt] OR practice guideline[pt] OR consensus development conference[pt] OR consensus development conference, NIH[pt] OR position statement*[tiab] OR policy statement*[tiab] OR practice parameter*[tiab] OR best practice*[tiab] OR standards[ti] OR guideline[ti] OR guidelines[ti] OR ((practice[tiab] OR treatment*[tiab]) AND guideline*[tiab]) OR CPG[tiab] OR CPGs[tiab] OR consensus*[tiab] OR ((critical[tiab] OR clinical[tiab] OR practice[tiab]) AND (path[tiab] OR paths[tiab] OR pathway[tiab] OR pathways[tiab] OR protocol*[tiab])) OR recommendat*[ti] OR (care[tiab] AND (standard[tiab] OR path[tiab] OR paths[tiab] OR pathway[tiab] OR pathways[tiab] OR map[tiab] OR maps[tiab] OR plan[tiab] OR plans[tiab])) OR (algorithm*[tiab] AND (screening[tiab] OR examination[tiab] OR test[tiab] OR tested[tiab] OR testing[tiab] OR assessment*[tiab] OR diagnosis[tiab] OR diagnoses[tiab] OR diagnosed[tiab] OR diagnosing[tiab])) OR (algorithm*[tiab] AND (pharmacotherap*[tiab] OR chemotherap*[tiab] OR chemotreatment*[tiab] OR therap*[tiab] OR treatment*[tiab] OR intervention*[tiab])))

maintenance of its half-life greater than 6 hours and also includes the criteria of absence of anamnestic response for total response[28].

The Argentine guidelines from the *Fundación de la Hemofilia* recommends FVIII, 20-50 IU/kg, three times a week for patients with low-responding inhibitors. Increase dose or reduce application intervals if the patient has frequent bleeding. Patients with high-responding inhibitors with a good prognosis may receive a scheme of FVIII, 50-100 IU/kg, three times a week, or a high-dose regimen. Patients with poor prognosis may use high-dose regimens (FVIII 100 to 200 IU/kg)[30].

In 2008, the Committee of Latin America on the Therapeutics of Inhibitor Groups (CLOTTING), composed by hemophilia specialists, published an ar-

Table 2. Summary of recommendations from Latin America countries, excluding Brazil.

Author	Publication year	Country	Scheme and doses	Response criteria
Argentine Society of Hematology [27]	2017	Argentina	ITI is recommended as a management strategy for patients with high titer inhibitors. No information about ITI schemes is provided.	No criteria defined.
Government of Chile. Ministry of Health. [28]	2013	Chile	Recommendation does not state an ideal dose, however, reports that high doses seem more effective when the maximum titer is >200 BU and, regardless of the titer, in all cases, the higher dose shortens the ITI times.	- Total response: titer undetectable (≤0.6 BU), recovery of >66% of the administered factor and/or maintenance of its half-life greater than 6 hours and absence of anamnestic response; - Partial response: high responder turns into low responder; - No response: no definition.
Government of El Salvador. Ministry of Health. [29]	2018	El Salvador	ITI defined as an intensive and repeated exposure to antigen.	- Total response: titer undetectable (≤0.6 BU) and normal pharmacokinetics; - Partial response: reduction of inhibitor titer (≤0.5 BU), without normal pharmacokinetics and absence of anamnestic response over a long time period; - No response: absence of success criteria after thirty-three months of uninterrupted treatment or demonstration of failure in the progressive reduction of 20% of the inhibitor titer after successive controls every six months of ITI.
Fundación de la Hemofilia [30]	2021	Argentina	Patients with low-responding inhibitors: FVIII, 20-50 IU/kg, three times a week. Increase dose and/or reduce application intervals if the patient has frequent bleeding. Patients with high-responding inhibitors with a good prognosis: FVIII, 50-100 IU/kg, three times a week, or a high-dose regimen. Patients with high-responding inhibitors with a poor prognosis: high-dose regimens (FVIII 100 to 200 IU/kg).	- Total response: titer undetectable (≤0.6 BU) and normal pharmacokinetics; - Partial response: reduction of inhibitor titer (≤0.5 BU), without normal pharmacokinetics and absence of anamnestic response after 6-month treatment or 12-month prophylaxis; - No response: absence of success criteria after 33 months of uninterrupted treatment or demonstration of failure in the progressive reduction of 20% of the inhibitor titer after successive controls every six months of ITI.

ITI: immune tolerance induction; BU: Bethesda units.

ticle based on clinical practice and literature review regarding the diagnosis and treatment of CHAWI, from the regional perspective. The authors reported that ITI is recommended for high-responder inhibitor patients. They cited two strategies that are used for ITI in Latin America: a modified high-dose regimen and the low-dose Dutch regimen with a dose of 30 IU/kg of FVIII/von Willebrand factor (VWF) concentrate three times per week. However, no specific recommendations are proposed in the publication[31].
A case report of ITI in a pediatric patient with hemophilia from Costa Rica, published in 2018, described the use of FVIII in a low-dose regimen with 750 IU (50 IU/kg) Monday - Wednesday - Friday, inhibitors titers of 0.8 BU/mL six months later and a FVIII recovery test in the normal range in the 8th month of ITI. ITI was performed through a one-year period until the FVIII inhibitor titer showed to be undetectable[32].

Economic issues and access to treatment

An important issue for patients with hemophilia and HTI is the disease-related economic burden. Resource utilization and costs among patients with inhibitors may be up to 3-fold higher than those without inhibitors[33,34].
ITI cost-effectiveness evaluation is controversial, since outcomes depend on the intensity of dose regimen and the type of concentrate used, leading to more or less favorable results regarding on-demand or prophylactic therapies[35]. Kenet et al., 2017, developed an economic model to compare high dose ITI versus low dose ITI associated with bypassing agent prophylaxis and concluded that low dose regimen is cost-saving with the potential of morbidity reduction[36].
Most patients diagnosed with hemophilia receive inadequate treatment worldwide, which is especially observed in low and middle-income countries. WFH analyzes the quality of assistance through per capita FVIII use and defines ≥ 1 IU per capita per year as the minimum to guarantee patients' survival and ≥ 3 IU per capita per year as the minimum to keep articular function and reach quality of life similar to healthy individuals[1,37].
Mean utilization of FVIII in Brazil was estimated at 4.309 IU/capita in 2019, the third highest among upper middle-income countries from Americas. Although higher than established minimum indexes, it is still below those of high-income countries. Values observed for Canada and United States in the same year were 8.774 IU/capita and 7.105 IU/capita, respectively[1].
Although patients need multidisciplinary and complete attention in the management of hemophilia, costs related to the coagulation factors acquisition correspond to 90% of the total expenses[38]. In Brazil, the Unified Health System (Sistema Único de Saúde - SUS) is a public healthcare system that promotes universal preventive and curative care to the whole population, following the principles of universality and equity[39]. Thus, the treatment of hemophilia A is offered to all disease population, at no cost to patients. Considering that ITI proposes high-doses of FVIII for a prolonged time, strategies to decrease disparities and to promote equity must be proposed worldwide[8].
Although only low quality data is available, no statistical significant differences are observed between low dose (50 IU/kg of factor VIII concentrate three times per week) or a high dose (200 IU/kg of factor VIII daily) in ITI regimens[40]. This was one of the aspects considered in the development of the ITI protocol in Brazil, in addition to economic issues.

How is ITI proposed in Brazil?

In 2015, the Brazilian Ministry of Health published two documents to provide general recommendations on hemophilia A management: "Hemophilia Manual" and "Protocol for ITI Use in Patients with Hemophilia A and Inhibitor"[3,41]. Table 3 and figure 2 show, respectively, the characteristics of patients eligible for ITI and the recommended treatment schemes in Brazil.
Patients eligible for ITI in Brazil are those with persistent high responding inhibitor for at least six months, proven through at least two consecutive dosages -with a 2-4-week interval- and greater than >0.6 BU/mL, using bypassing agents (aPCC or rFVIIa) to control or prevent bleeding events. In addition, it is recommended that the protocol starts when inhibitor quantification is <10 BU/mL, patients present a favorable evaluation from a multidisciplinary team regarding the coagulation factor concentrate infusion, and test results (blood count, research and titration of inhibitor, urea and creatinine, transaminases, alkaline phosphatase, gamma glutamyl transferase, prothrombin time, albumin, globulins, and

routine urinalysis). The guardian should also sign an informed consent, and patients, parents, or responsible need to commit to record all infusions in their own diary and return it to the treatment center in a maximum period of two months[41].

In Brazil, ITI treatment follows an escalating rationale, as shown in figure 2. All patients fulfilling inclusion criteria reported above are eligible to initiate low-dose scheme using FVIII 50 IU/kg, three times a week. When the absence of a decline in inhibitor titer with a low-dose regimen of at least 20%, in every six-month period after the beginning of ITI, is observed, it is recommended to initiate high-dose scheme using FVIII 100 IU/kg every day (Figure 2). It is also recommended that the treatment must be performed with the FVIII concentrate previously used, whether plasma or recombinant origin[41].

The national scenario was evaluated in the Brazilian Immune Tolerance (BrazIT) study, aiming to investigate predictors of response to ITI regarding the protocol recommended by the Ministry of Health. The study included patients with confirmed diagnosis of hemophilia A with active inhibitor, which were not selected based on favorable risk factors. All patients started ITI with a low-dose regimen (50 IU/kg, three times a week). Upon lack of response (no decline of inhibitor of at least 20% of peak levels within six months after ITI start), a high-dose regimen (100 IU/kg daily) and subsequent change to plasma-derived FVIII for those who started on recombinant FVIII was recommended. The study outcome, response, was defined based on inhibitor titer, FVIII half-life, and recovery. Preliminary and extended results suggest that a low-dose regimen is effective for most patients[42,43].

In preliminary results, 45 patients from four hemophilia treatment centers in Brazil were assessed. Most patients responded to ITI (85%), and 15% failed despite changing to high-dose regimen. Factors associated with treatment failure were having inhibitor peak during ITI (p=0.004), change to high-dose regimen (p=0.0001), and having more breakthrough bleeding events (p=0.012). Patients who failed to treatment also had a longer ITI duration than those classified as successful (3.3 vs 1.6 years; p=0.0002)[43].

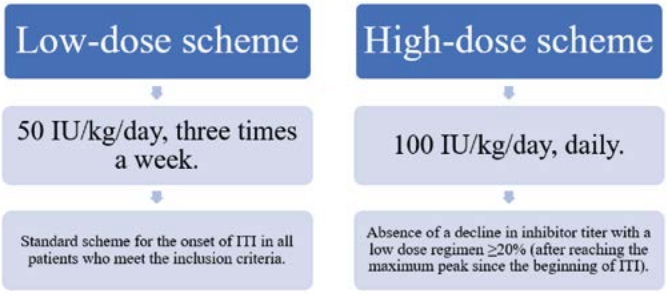
Extended analysis of study data assessed 88 patients from nine hemophilia treatment centers in Brazil. This analysis showed that most patients responded to ITI (77.8%) and 22.2% failed despite changing to high-dose regimen. Factors associated with response to treatment were: age (p=0.032), levels of

Table 3. Inclusion criteria for immune tolerance induction treatment among patients with hemophilia A in Brazil.

Characteristics	Recommendations
Inhibitor	Persistent inhibitor for at least 6 months, proven through at least two consecutive dosages - with a 2-4-week interval.
Inhibitor level	>0.6 BU/mL
Bypassing agents	Patients must be using bypassing agents (partially activated prothrombin complex concentrate or recombinant activated factor VII) to control bleeding events.

BU: Bethesda units.

Figure 2. Recommended immune tolerance induction treatment schemes for congenital hemophilia A with inhibitors patients in Brazil.



IU: international units; ITI: immune tolerance induction.

inhibitor immediately before ITI start (p=0.005), inhibitor peak levels during ITI (p< 0.001), change of ITI treatment (p< 0.001) and suffering breakthrough bleeding during ITI (p< 0.001)[42].

None of the studies above specifically mention the hemophilic pediatric population. Considering that the inhibitor develops in the first 20 days of exposure, this population is expected to be the most impacted[4,5].

Conclusion

Development of HTI among patients with hemophilia A is one of the main complications observed during disease management. ITI is considered the standard of care to eradicate such inhibitors. However, high costs and disparities in access to medication are challenges in clinical practice and decision-making process.

There is a need for more studies to better understand ITI in the hemophilic pediatric population in Brazil and Latin America countries. This is a significant population and a successful treatment at a younger age could have a positive impact in their adult life.

Although developed countries used to propose the initial use of high-dose protocols, the recent analysis from international collaboration proposes low dose protocol to very good and good prognosis patients[44]. The Brazilian scenario is still in the process of scientific base construction, the ITI program has less than seven years since implementation and needs more evidence, especially in a real-world scenario. However, considering the efficacy of this initial data of escalating regimen[41], which allowed costs reduction and consequently that more patients could have access to treatment. Brazilian experience should be used in other low and middle-income countries in the management of patients with inhibitors, in an attempt to improve healthcare and equity for the hemophilic pediatric population.

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Authors' contributions

Authors' contributions C.M.S. Pinto and F.F. Carvalho defined the scope of publication, interpreted data and wrote the manuscript. C.M.S. Pinto and L. M. Silva screened the studies and analyzed the data. All authors critically revised the manuscript and revised critically the work providing substantial input and gave final approval of the version to be published.

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Conflicts of interest

CMSP provides speaker and consulting services for Takeda, NovoNordisk and Roche, and consulting services for Bayer, CSL-Behring and Sanofi-Aventis. FC and LMS are Takeda Pharmaceuticals full time employees

ORCID

Christiane Maria da Silva Pinto - 0000-0003-1834-7179

Liliana Martins da Silva - 0000-0001-6703-7498

Fabio Ferreira de Carvalho Jr - 0000-0002-2127-5498

Conflictos de interés: Christiane Maria da Silva declara haber recibido honorarios por parte de Takeda, NovoNordisk, Roche, Pfizer, CSL-Behring, Bayer y Sanofi-Aventis por conferencias y actividades educativas en las que ha participado. Fabio Carvalho declara ser empleado de Takeda Pharmaceutical y posee acciones en la bolsa. Liliana Martins da Silva declara ser empleada de tiempo completo de Takeda Pharmaceuticals.

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