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ORIGINAL ARTICLE

Immunotolerance induction effectivity in hemophilia A children and neutralizing alloantibodies

Efectividad de inducción de tolerancia inmune en niños con hemofilia A y aloanticuerpos neutralizantes

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What do we know about the subject matter of this study?

Within the medical field, knowledge about hemophilia, its treatment, and complications is limited given that it is a very rare condition. Currently, the presence of inhibitors is the most severe complication and, in order to raise interest in it, our study reports a local experience that had success in its management.

What does this study contribute to what is already known?

This study shows that a complex treatment, such as Immune Tolerance Induction in patients with hemophilia A and inhibitors, is currently possible in our country with similar results to those of centers with the highest standards of care of this disease worldwide.

Abstract

The development of anti-factor VIII neutralizing antibodies in hemophilia A is the most severe complication related to treatment. Immune tolerance induction (ITI) is the only known treatment for eradicating inhibitors. A successful ITI allows using factor VIII (FVIII) again for the treatment or prophylaxis of hemorrhagic events. **Objective:** To report the experience of pediatric patients who underwent ITI in the country's public health care network. **Patients and Method**: Retrospective and descriptive analysis of 13 pediatric patients with severe Hemophilia A and high-titer inhibitors persistence who underwent ITI and complete follow-up. Plasma-derived FVIII concentrate was used at 70-180 IU/kg/day doses. The success of the treatment is defined by achieving a negative titer and a half-life recovery of the FVIII. The results were expressed in median (range). **Results:** In 13 patients, the inhibitor was identified at an average age of 17.6 months, after 35.2 days of exposure to the FVIII. 11 patients (84.6%) recovered the half-life of FVIII after 49.6 months of treatment. In the patients who responded to treatment, the inhibitor titer was negative at 6 months on average. **Conclusions**: ITI is the treatment of choice for patients with hemophilia A and inhibitors persistence. ITI must be personalized since the time response is variable in each patient.

Keywords:
Hemophilia A;
immune tolerance induction;
inhibitor;
factor VIII;
neutralizing antibodies

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Introduction

Hemophilia A (HA) is the most common serious inherited clotting disorder caused by Factor VIII (FVIII) deficiency. Replacement therapy is the preventing treatment for recurrent bleeding and the successful resolution of bleeding events in these patients. The development of neutralizing antibodies (inhibitors) against FVIII is currently the most serious complication of treatment. Its appearance is more frequent in HA than in hemophilia B, and in severe patients with < 1%FVIII/FIX, compared with those of moderate to mild status. This complication can occur at any age, but especially in children, and after the first 10 to 15 exposures to exogenous FVIII. It presents a general frequency of 20-30% in hemophilia A[1-5].

There are two ways of managing patients with hemophilia and inhibitors. The first one focuses on the eradication of these antibodies, with a long-term treatment called Immune Tolerance Induction (ITI). The second one is the management of acute bleeding events through the so-called bypassing agents, until immunotolerance achievement[1,5-7].

To date, the ITI is the best therapeutic alternative for patients with exogenous FVIII inhibitors. It guarantees an effective future replacement therapy for treating bleeding events and allows for the implementation of prophylactic regimes that prevent sequelae such as arthropathy and life-threatening bleeding, improving quality of life. This therapy is based on the administration of high FVIII doses, regularly for a period of months to years, in order to make the immune system tolerant to the antigen and prevent the future production of new antibodies, and it can also be performed at any age. This treatment presents a success rate between 60 and 80%[8-12].

In 1970, the first use of ITIs was reported in Germany in a patient with Hemophilia A and high-titer inhibitors who was able to initiate FVIII prophylaxis after 24 months of ITIs, resulting in an improvement in his musculoskeletal status and decreased morbidity[13]. To date, several publications have reported the prognostic factors involved in the outcome of treatment with immune tolerance (table 1)[14-19].

Since 2008, the *Hospital Roberto del Río*, a national reference center for hemophilia in Chile's public health network, has started the ITI treatment in the pediatric population with hemophilia A and inhibitors. Our objective was to characterize a cohort of children with severe hemophilia A and persistent high-titer neutralizing antibodies treated with immune tolerance and report related risk factors and outcomes of this intensive treatment.

Patients and Method

Study design and patient selection

Retrospective, descriptive study of a group of patients with severe hemophilia A (FVIII < 1%) and inhibitors, who were under ITI regimen from September 2008 to September 2018. The protocol was approved by the Research Ethics Committee of the Northern Metropolitan Health Service. All patients included in the treatment regimen are high responders, in other words, with inhibitor titers at some point in their pretreatment course > 5 UB/ml. Before starting the therapy, parents/guardians were informed about the intensity of the treatment and signed an informed consent form.

ITI regime

At first, all patients received the ITI regime daily. Doses depended on the availability of FVIII in the country, with an average of 100 IU/kg. In this treatment, we used plasma-derived FVIII concentrates, with high levels of von Willebrand factor (pdFVIII/VWF), using the same product which had generated the appearance of inhibitors (Fandhi®, Alphanate®, both from Grifols®). A central venous catheter was placed to administer the concentrate depending on the difficulty in guaranteeing vascular access. The immune tolerance began when titers were below 10 UB/ml, as internationally recommended.

Laboratory follow-up and definition of success

Periodic inhibitor titer monitoring was performed every 8 weeks until the value was < 0.5 UB/ml. Once this inhibitor clearance was reached, an FVIII recovery study was performed every 4 weeks, expecting a level higher than 66% of plasma FVIII at the time of infusion. Once this percentage was achieved, a pharmacokinetic study was performed every 8 weeks to establish half-life recovery. Table 2 shows the definitions of response to ITIs[8,11,18,20]. In those patients who received daily doses of ITI, once they reached an FVIII over

Table 1. Suggested Poor Prognostic Factors for ITI

Inhibitor titre before ITI >10BU
Historical peak titre >200BU
Titre peak during ITI >200BU
Age > 8 years at the start of ITI
Latency at start of ITI > 5 years
Interruption in ITI >2 weeks in duration

ITI: Immunotolerance induction, BU: Bethesda Units.

Table 2. Definitions of treatment result with ITI

Success	Negative inhibitor titre. Normal FVIII half-life at 6 hours after a 72-hour washout period. Plasma levels of FVIII >1% 48 hours after a dose 50 IU/Kg
Partial Response	Negative inhibitor titre, no normal FVIII half-life, no anamnestic response or FVIII level maitained >1% receiving daily doses. Allows to leave prophylaxis.
Failure	Persistence of inhibitor titres, failure of the inhibitor to decline by ≥ 20% during the next 6 months after three months of ITI initiation or failure to achieve tolerance after 33 months on ITI.

FVIII: factor VIII, IU: international units.

66% post-infusion of 50 UI/Kg, and after a half-life recovery higher than 25%, the administration frequency of ITI was reduced to alternate days, in agreement with the parents, maintaining the same dose, in order to increase the tolerance to this intense treatment.

Treatment of bleeding events during ITI

When the patient presented ≧ 5 UB/ml, we used the bypassing agents recombinant activated factor VII (rFVIIa) 120-180 ugr/Kg/dose and activated prothrombin complex concentrate (aPCC) 50-100UI/Kg/dose. The frequency of treatment was assessed individually according to clinical response. If there was no clinical response with one agent, the other one was used, and occasionally both agents were administered sequentially according to international recommendations (21,22). Once patients had decreased their inhibitor titers to <5UB, the FVIII was used for hemorrhagic events at doses that would neutralize the inhibitor titer every 4 to 6 hours. The results were expressed as median (range).

Results

Table 3 shows the demographic and clinical characteristics before starting the treatment. 14 patients with hemophilia A and persistent high-titer inhibitors were admitted to ITI regimens. One patient left treatment 9 months after it started, with inhibitor titers still > 5 UB, and did not continue the follow-up in our center, being the only patient excluded from the analysis.

The age at which the inhibitor was identified was 17.6 months (2-48), after 35.2 days (9-112) of administration of pdFVIII/VWF. It was not possible to obtained data on the number of days of factor administration before the appearance of the inhibitors in two patients. The age at the beginning of the ITI regime was 3.1 years (0.6-8.0) and the ITI latency time after the identification of inhibitors was 19.6 months (5.5-44).

Table 3. Clinical and demographic characteristics of patients treated with ITI

Case No.	Age at Dg of inhibitor (months)	F8 gene mutation	CDE to FVIII (days)	Titre at Dg (BU)	Age at start of ITI (years)	Time from Dg to start of ITI (months)	Highest historical titre pre-ITI
1	13	Frameshift	16	0.6	2.01	12.13	7.2
2	32	Int 22 inv	79	10	4.31	21	10
3	19	Int 22 inv	16	18	1.94	6	18
4	19	Nonsense	112	40	4.19	32.4	40
5	2	Int 22 inv	20	16.2	0.59	5.5	16.2
6	16	Int 22 inv	NA	26	3.51	14.4	26
7	4	Exon Del	9	4.8	1.08	10.2	17.6
8	17	Int 22 inv	20	146	3.51	10.2	146
9	15	Nonsense	50	140	2.7	25.6	146
10	17	Exon del	12	42	2.8	17.1	143
11	15	Int 22 inv	30	8.4	4.1	34.6	8.4
12	12	Int 22 inv	25	384	1.59	8.3	384
13	18	Int 22 inv	42	1240	4.2	33.6	1240
14	48	Int 22 inv	NA	13.5	8	44	54

Dg: diagnosis, CDE: cumulative days of exposure, NA: not available, FVIII: factor VIII, ITI: Immunotolerance induction, BU: Bethesda Units, Int 22 inv: Intron 22 inversion, Exon del: Exon deletion.

Six patients required a central venous catheter (Port-a-Cath®) and none of them completed their treatment using this route. In 3 patients, the line had to be removed due to infection. Two patients used a percutaneous catheter during the first year of treatment and the rest of the time used a peripheral catheter (by direct venous puncture) to administer treatment from the beginning.

Table 4 shows a description of the most important aspects of ITI treatment by each patient. All patients started their treatment with values < 10UB and the doses ranged from 70 to 180 IUI/Kg/day. Seven patients switched to alternate-day ITI scheme.

Two patients discontinued therapy after a year upon parental decision. Both had inhibitor clearance at the time of suspension but had not achieved normalization of FVIII half-life. 18 months later, they resume the ITI regime due to frequent bleeding episodes and, although the inhibitor titer had risen, it remained at <5UB. The same pdFVIII/VWF concentrate was used for this new round of treatment, at doses around 86-88 IU/Kg three times a week. Both patients reach normalization of half-life at 20 and 24 months later, respectively.

Only 2 patients with hemorrhagic phenotype received prophylaxis with bypassing agents during the ITI regime.

Regarding the distribution of mutations of the FVIII gene, all of them correspond to null mutations, which present a higher frequency of inhibitors.

Out of the 13 patients with complete evaluation, 2 did not respond to ITI therapy and 11 recovered the half-life of FVIII at 49.6 months (26-70), so the success of ITI in this series was 84.6%. In those patients who responded, the inhibitor clearance appear after 7.3 (1-20) months on average, allowing early discontinuation of bypassing agents. Out of the 11 children who achieved immune tolerance, none presented a historical titer > 200UB, unlike the 2 patients who did not respond, who at some point in their lives presented values higher than the risk cut-off.

All patients started their treatment with < 10UB and all of them were under 8 years old. Three patients presented a time between the diagnosis of inhibitors and the start of ITIs longer than 24 months, one of them did not respond.

rFVIIa and/or aPCC were used in all bleeding events during the ITI treatment period, depending on the history of response with one or another of these agents in previous bleeding episodes. All events responded to treatment and there were no thrombotic complications.

Intracranial hemorrhage in one patient two months after starting the immune tolerance therapy was the only serious event, which was managed with rFVIIa with good response and no sequelae.

Table 4. Follow-up and ITI treatment outcomes

Case No.	Highest titre during ITI (BU)	Titre at start ITI (BU)	ITI dose (IU/Kg/d)	Time to negative BU (months)	Half-life recovery time (months)	Treatment outcome
1	6.2	7.2	130	1	26+	E
2	30	3	88	4	60*	E
3	110	1.3	154	8	42	E
4	18.3	5	86	15	52+	E
5	11.9	1.7	136	2	55+	E
6	36.9	3.5	70	12	70+	E
7	76	1.2	180	3	26+	E
8	140	3.5	86	20	59*	E
9	82	2	76	6	39	E
10	176.4	0	75	4	66+	E
11	19	1.1	107	5	51+	E
12	1.190	9	108	S/R	S/R	F
13	50	2.1	100	S/R	S/R	F
14	300	4	100	NE	NE	NE

BU: Bethesda Units, NE: Not evaluated due to permanent withdrawal from ITI, N/R: no response, S: success, F: failure. +Change in frequency of ITI once half-life partially achieved. *Abandoned treatment and restarted ITI.

After successful completion of the ITI regime, all children were changed to a prophylactic regimen of pdFVIII/VWF on alternate days or three times a week depending on their pharmacokinetics. The dose was gradually decreased, until the usual prophylaxis regimen for patients with severe hemophilia A was reached at 20-30 IU/kg, ensuring an FVIII level > 1.5% at 48 or 72 hours.

There were no relapses in patients who have completed their ITI treatment.

Discussion

Inhibitor eradication is the standard treatment worldwide for patients with Hemophilia A and inhibitors. The different ITI schemes used are aimed at generating recognition of the infused FVIII as owned by the patient, allowing effective treatments with the factor concentrate in deficit and, in addition, to allow the implementation of prophylactic regimes.

The decision of the treatment scheme depends on different variables. First is access to treatment, i.e. the amount of FVIII concentrates available in the center or country; second is the willingness of parents to follow such intensive treatment, and third is the availability of adequate vascular access. In patients with poor venous access, such as infants and young children, it may be necessary the use of a long-term central venous catheter, with all the aspects that it entails.

The difference between these diverse regimes is the time it takes to achieve a normal half-life of FVIII. With a high-dose regimen, we will achieve immune tolerance in a shorter period, which is why it is currently the recommendation in those patients with a very hemorrhagic phenotype. This last recommendation would be a fourth variable to consider for the choice of ITI scheme in those countries where resources are available to perform it. We used a variable dose scheme adjusted to the weight of the child, the presentation of the product (the highest concentration vials available are 1,000 IU/10 ml), the venous access, and the availability in the country of the concentrate.

Among the factors that are proposed as a good prognosis for ITI, one of the most powerful has been the start of ITI with less than 10 UB and a historical peak of inhibitor < 200 UI. Regarding our cohort, we can say that the two patients who did not respond to ITI after two years of intensive treatment were those who presented a historical titer > 300 UB, since the rest of the variables involved are distributed without difference in the rest of the patients, and all started their treatment with a titer lower than 10 UB.

In our cohort, we observed that the modification of the immune tolerance scheme once started, does not affect the final result. After reaching clearance and a 25% recovery of half-life, we were able to modify the treatment regimen and, in addition, manage bleeding episodes with high doses of FVIII and intercurrent surgeries. The presence of some flexibility allows better tolerance to the treatment by the patient and family.

This treatment was successful in 84.6% of cases, which in our opinion is a very good result when comparing with previous international publications. We also believe that it is, in part, due to the use of plasma-based concentrates. This observation is based on the results described by the SIPPET study, the only prospective, randomized study that compares the immunogenicity of plasma-derived FVIII concentrates versus recombinant FVIII ones[23].

This study showed that the use of plasma-based concentrates not only showed a lower rate of high-titer inhibitors but also that the historical peak was lower when this occurred. Table 1 shows that both variables determine factors of a better prognosis.

There are reports on the benefit of using pdFVIII/VWF as a rescue treatment in those ITIs that showed no response with the use of recombinant FVIII concentrate, which would reinforce the observation above[24].

As long as there is no response to the factor in deficit, acute bleeding events can be managed with the bypassing agents rFVIIa and aPCC. The mechanism of action of these two concentrates lies in enhancing the hemostasis processes through alternative pathways, however, they present several disadvantages such as an unpredictable response, which may lead to untreatable life-threatening bleeding or cause significant sequelae.

In addition, there is no laboratory test for following-up patients, therefore, the effectiveness of treatment is only measured clinically. Finally, the costs of this therapy far exceed those of classical replacement therapy[25].

Recently, a monoclonal antibody has been approved for prophylaxis schemes in hemophilia A and inhibitors that presents a very good response, which significantly decreases the number of bleeding events. The development of this new therapeutic tool is under discussion, and it would be an alternative proposed as prophylaxis in those patients with inhibitors who have a hemorrhagic phenotype while achieving immune tolerance. In our opinion, this new treatment does not replace ITI, since it is not useful for the management of acute bleeding events, in which bypassing agents should be used. We also know that the best scenario for a patient with inhibitors is their eradication and the possibility of using the deficit factor in usual doses and frequencies.

Despite the limitations of a small case-cohort, in addition to the limitations of a descriptive study, we

believe that our results are valuable, as they correspond to a 10-year follow-up of a complex treatment, which allows us to eliminate the major current complication in the treatment of patients with hemophilia, with a high response rate.

Conclusion

ITI is the treatment of choice for patients with hemophilia A and inhibitors. The results of our cohort of patients treated with pdFVIII/VWF are very good, allowing inhibitor clearance within 7.3 months approximately after starting treatment and around 85% of final success rate. Immune tolerance must be performed according to each patient and the response time is variable in each one. An inhibitor titer higher than 200 UB can be considered a threshold of poor response.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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