

Immune Tolerance Induction in Hemophilia A

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INTRODUCTION

The induction of immune tolerance (ITI) is the only proven strategy for the eradication of persistent inhibitors, with a success rate of 60 to 80% with different regimens. Different treatment protocol options are used, although there is no consensus on what product or dose to use. The main predictors for the success of ITI are the early age of onset, a historical peak titer less than 200 Bethesda units (BU) and titer inhibitor less than 10 BU prior to the start of ITI. The anamnestic increase in inhibitor titer and inhibitors > 5 years from diagnosis are associated with poor prognosis.

METHODS

From 1997 to 2009, 7 patients with hemophilia A (HA) (6 severe HA and 1 moderate HA) and persistent inhibitors started ITI in our department (table 1).

Table 1- Evaluation of patient before starting ITI

Patient	Year of birth	Type of Haemophilia	Age at beginning of hemophilia treatment	Type of product used	Days of exposure to FVIII	Time since 1 ^o detection of inhibitor to ITI	Titre pré-ITI (BU)
1	25-10-1988	HA severe	2 years	Monoclonal	>150	28 months	3
2	07-10-1935	HA moderate	38 years	Plasma-derived	>150	4 months	32
3	16-05-1967	HA severe	5 years	Plasma-derived	>150	21 years	2
4	21-05-2000	HA severe	17 months	Recombinant	<50	11 months	2
5	18-10-2000	HA severe	>1 month	Recombinant	<30	6 months	30
6	04-01-2004	HA severe	19 months	Recombinant	<50	2 months	7
7	18-12-2007	HA severe	9 months	Recombinant	<30	1 month	9

RESULTS

Time to ITI response ranged from 3 to 28 months. A prolonged time (>2 years) and a high anamnestic response (>200 BU) were observed in patients 3 and 7 (table 3).

Patient 3 began ITI with 100 UI/kg/daily, at age 33, after 20 years of inhibitor presence and multiple exposures to factor VIII (FVIII).-A high anamnestic peak (412 BU) was observed, he had a good response after 24 months but he relapsed 6 months after the end of ITI.

Patient 7 began ITI at the age of 15 months, after a low number of previous exposure days (<30) and a titer inhibitor lower than 10U prior to the start of ITI. A high anamnestic peak was observed (255 BU), with the need to change the dose and frequency of factor (200UI/ Kg daily). Only a partial response was observed in patient 7 after 28 months (clinical response, absence of inhibitor, FVIII activity recovery of 57% and FVIII half-life of 5h after 72h washout period). He is currently receiving prophylactic treatment, with a good clinical response.

Patient 5 also relapsed after more than 2.5 years, having restarted ITI with plasma derived FVIII and has shown a good response (table 3)..

CONCLUSION

Out of 7 patients who started ITI, 4 had sustained responses, 1 had a partial response 1 relapsed and restarted ITI with good response, and 1 relapsed after 6 months, maintaining the inhibitor present. Only one patient out of the 7 who initiated ITI persists with an inhibitor, corresponding to a success rate of 85%. Although there is still no consensus on the best regimen to use, it has been suggested to use higher doses of FVIII against inhibitors in the presence of high responders, which is confirmed in this review. In addition, our experience suggests that the primary prognostic factor is the intensity of the anamnestic response.

AIM

The aim of this study was to evaluate the doses and products used in our patients receiving ITI, as well as its evolution.

The doses ranged from 50 IU/kg 3x/week to 200 IU/kg daily. In 5 cases, ITI was used with the same products and 3 cases switched to a different product (table 2).

Table 2 – ITI regimens used in the patients

Patient	Year of ITI	Age at ITI	Titre pré-ITI (BU)	Product previously used	Product used in ITI	Initial dose (U/Kg)	Frequency
1	1997	8 years	3	Monoclonal	Plasma-derived	100	1x/day
2	2000	65 years	32	Plasma-derived	Plasma-derived	100	1x/day
3	2000	33 years	2	Plasma-derived	Recombinant	100	1x/day
4	2003	2 years	2	Recombinant	Recombinant	50	3x/week
5	2004	3 years	30	Recombinant	Recombinant	50	3x/week
6	2007	3 years	7	Recombinant	Plasma-derived	50	3x/week
7	2009	15 months	8	Recombinant	Plasma-derived	90	3x/week

Table 3 – Patients response to ITI

Patient	Anamnestic peak of inhibitor	FVIII: activity at the end of ITI	Titre of inhibitor at the end of ITI (BU)	Duration of ITI (month)	Relapsed
1	32	>66%	0	3	No
2	32	>66%	0	6	No
3	412	>66%	0	24	Yes (after 6 months)
4	14	>66%	0	15	No
5	20	>66%	0	21	Yes (after 2.5 years)
6	60	>66%	0	8	No
7	255	<66%	0	28	No

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