Risk factors associated with high-titre Inhibitors development in Previously Untreated Hemophilia A patients (PUPS-HA) born between 2000 and 2013: a single center experience

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INTRODUCTION AND OBJECTIVES

High-titre inhibitors (HTI) development is the most serious and costly complication of FVIII replacement therapy in previously untreated patients (PUPS) with haemophilia A (PUPS-HA).

Several non-modifiable (F8 genotype, family history of inhibitors, ethnicity, differences in immune response etc.) and environmental or potentially modifiable factors (number of exposure days, treatment regimen, intensity of first treatment, type of FVIII product and danger signals) may determine the final risk. Since 2007, Venezuela started a primary prophylaxis program, Canadian modified regimen using second-generation full-length rFVIII (FLrFVIII). The objective of this study was to evaluate the incidence of HTI and possible associated risk factors in PUPS-HA treated in our Center

PATIENTS AND METHODS

Retrospective study, included PUPS-HA with FVIII < 0.02 UI/mL^{-1} born between 2000 and 2013. A total of 221 were registered, 165 with FVIIIC < 0.01 IU/mL $^{-1}$ and 56 with 0.01-0.02 IU/mL^{-1} , 11 were excluded because being treated in another centers. Primary outcome was HTI development during the first 50 Exposure Days (ED). Inhibitor detection: Bethesda/Nijmegen assay, at least every 3 months, HTI if titre >5 BU. Patients were analyzed according to the type of FVIII used: Group 1 (FLrFVIII) 125 (59.6%), Group 2: plasma-derived FVIII (PD-fFVIII) 56 (26.6%) and Group 3: (Both products) 29 (13.8%). Other variables studied: age of diagnosis, family history of hemophilia or inhibitors, first FVIII treatment (age, indication and duration), age of HTI detection, ED before detection, type of regimen (prophylaxis/on-demand). Logistic multivariate regression and Kaplan Meier were used, 0.05 was considered as statistical significant, STATA 11.0 as the statistical package used.

RESULTS

A total of 95/210 patients developed an inhibitor (45%). Sixty 60/210 (28.5%) were a HTI and 35/210 (16.7%) a low-titre inhibitor (0.65 – 4.9BU). HTI in Group 1: 40/125 (32%), Group 2: 17/56 (30.3%), Group 3: 3 (10.3%).
Statistically significant variables were family inhibitors history (OR: 5.21 p: 0.001), age at first infusion (OR: 0.96 p: 0.03) and number of days of first treatment (OR:1.24 p:0.03).
Development of HTI was similar between patients treated with both types of FVIII products.

Table 1. Baseline characteristics of patients

	Group 1 r FVIII N:125 (59.6%)	Group 2 pd-FVIII N:56 (26.6%)	Group 3 Both products N:29 (13.8%)	Total N: 210
FVIII (UI/mL^{-1}) < 0.01 0.01 – 0.02 UI	93 (74%) 32 (26%)	43(77%) 13 (23%)	22 (76%) 7 (24%)	158 (75%) 52 (25%)
Age at diagnosis of hemophilia (months)	12.9±11.9 (0.5 - 84)	11.5±10.0 (0.3 -55)	19.1±16.2 (1 – 60)	13.4±12.4 (0.3 -84)
Family history of inhibitors n(%)	30 (24%)	16 (29%)	5 (17%)	51 (24%)
First treatment age (months)	15.2±12.7 (1- 84)	13.3±11.1 (0.6 -65)	19±15.1 (5 -60)	15.2±12.8 (0.6-84)
First treatment duration (days)	2.2 (1-19)	2 (1-10)	1.8 (1-6)	2.1 (1-19)

Table 2. Characteristics of patients with inhibitors

	Group 1 r FVIII N:125 (59.6%)	Group 2 pd-FVIII N:56 (26.6%)	Group 3 Both products N:29 (13.8%)	Total N: 210
Patients with inhibitors	65 (52%)	24 (42.8%)	6 (20.7%))	95 (45.2%)
Patients with HTI	40 (32%)	17 (30.3%)	3 (10.3%)	60 (28.6%)
Patients with low titre inh.	25(20%)	7(12.5%)	3(10.3%)	35(16.7%)
Age at HTI (months)	19.8 ±15.1 (3-60)	23.5 ±14.4 (4-48)	31.7 ±5.4 (24-36)	21.5±14.6 (3-60)
ED before development of HTI	19.4±14.7 (3-50)	18±18.8 (4-50)	17.6±11.5 (12-30)	18.4 ±11.4 (3-50)

Table 3. Analysis of risk factors associated to HTI

Variable	OR	p
Age of diagnosis	0.96	0.05
Type of product	0.81	0.25
Family history of hemophilia	1.51	0.22
Family history of inhibitors	5.21	0.001
Age at first FVIII treatment	0.96	0.01
Cause of the first exposure to FVIII	1.12	0.33
First treatment duration (days)	1.24	0.03
ED before development of HRI	0.97	0.67
Age at development of HRI	1.00	0.96
Primary prophylaxis	1.17	0.37

CONCLUSIONS

•High-titre inhibitors is a frequent complication in our PUPS-HA population, we found a cumulative incidence of inhibitors of 45%.

•Some genetic factors including ethnicity could explain this fact.

•The type of product was not a statistically significant risk factor, however it should be considered that pd-FVIII used in that period was a FVIII with low FVW content.

•As expected, development of inhibitors in our PUPS with HA seems to be a multifactorial phenomenon .

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