A Canadian survey on the incidence and risk factors for inhibitor development in severe hemophilia A PUPs: 2005-2010.

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Objective: Assessment of inibitor development (ID) in severe hemophilia A PUPs over a five-year period

Methods: All 26 Canadian hemophilia centers were approached. 18 centers had eligible patients and filled a questionnaire on their patients with severe hemophilia A (<0.02 IU/mL) born between September 1st 2005 and August 31st 2010

Results: 109 PUPs were identified. 89 of these had had at least 20 exposure days (ED) to Factor VIII (FVIII) or had developed an inhibitor. 27/89 (30%) developed an inhibitor which was of high titre (≥ 5 BU) in 19/27 (70%), and of low titre in 8/27 (30%). Inhibitors developed in 15/38 (39%) patients with an intron 22 inversion mutation and in 4/21 (19%) with low risk mutations. Dose-intensity (units/kg/d **X** ED) at time of first exposure was a strong predictor of ID (p = 0.02). Hemarthrosis and intracranial bleeding as the indication for treatment at first ED were associated with a 69% (9/13) and 63% (5/8) incidence of ID, respectively. Following the first ED, if patients were maintained *on demand* treatment, they had a 36% (17/47) incidence of ID, while if they were commenced *on prophylaxis* they had a 20% (8/40) incidence.

ID according to FVIII used was: Advate 16/50 (32%), Kogenate FS 10/28 (36%), Wilate 0/10, and Xyntha 1/1. Although the lowest incidence was with Wilate, it should be recognized that patients placed on Wilate were for the most part treated differently in other respects: vaccination was not administered in 8/10 of them during their first 20 ED and 5/10 were put *on prophylaxis* at time of first ED. Moreover none of the subjects treated with Wilate had a first bleeding episode that we found associated with a high risk of ID.

Results:

Further on subjects treated with Wilate

ID	Mutation	Indication first Rx	Dose-int first Rx*	Post-first Rx	Vaccine	ED
10	int 22	S. Tissue	3	Prophy	Yes	>50
22	stop	S. Tissue	3	Demand	No	>50
66	int 22	Prophy	1	Prophy	No	>20
67	small del	H. Bump	2	Demand	No	>20
96	missense	S. Tissue	2	Prophy	No	>50
97	int 22	S. Tissue	3	Demand	No	>50
98	int 22	Mucosal	1	Prophy	No	>50
99	int 22	S. Tissue	2	Demand	No	>50
100	splice site	S. Tissue	2	Demand	No	>50
105	stop	S. Tissue	2	Prophy	Yes	>50

*Dose-intensity of first treatment expressed in quertile for the whole sample size of 89 subjects

Conclusions: Cumulative incidence of ID during the first 20 ED to FVIII in an unselected Canadian population of severe hemophilia A PUPs was 30% with wide variations related to FVIII gene mutations but also apparently related to environmental factors (choice of FVIII, intensity of exposure, early initiation of prophylaxis). Further studies with careful attention to environmental factors are warranted.

DOI: 10.3252/pso.eu.WFH2012.2012