Does a once weekly prophylaxis with low dose factor VIII in PUPs with haemophilia A decrease the risk of inhibitor development? First results of a survey in centers of the Competence Network Hemorrhagic Diatheses East

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Objective

Inhibitor formation against factor VIII (FVIII) in patients with severe haemophilia A (HA) is a complex, multi-factorial process. Recently published data suggest that an early start of prophylaxis with once weekly application of 25 IU FVIII/kg decreases the risk of inhibitor development (1). Early intensive treatment was already identified as one of the danger signals for inhibitor formation (2). It has been suggested that recombinant (r)FVIII products are more immunogenic than plasma-derived (pd) products which was not confirmed by a just recently published large retrospective study (3). This multicenter retrospective cohort study was designed to describe the relationship between treatment characteristics and inhibitor development in PUPs with HA.

Design & Method

A survey in all pediatric centers of the KHDO was performed and the following data from PUPs with HA diagnosed from 2006 to 2011 were collected: age at diagnosis and at start of prophylaxis, FVIII gene mutation, body weight-related dose and frequency of FVIII application, number of exposure days (ED), danger signals and details to immune tolerance induction (ITI).

Results

Tab. 1: Disease severity and number of PUPs

Total	Severe	Mode-rate	Mild	Sub
91	49	6	23	13

Twelve KHDO centers treating children with HA participated in this survey. Data of 91 PUPs were included (tab. 1). Forty-four (90%) out of 49 patients with severe HA (sHA) had more than 50 ED. In sHA an inhibitor was detected in 30% (9/30) of patients receiving prophylaxis once weekly with 25 IU FVIII/kg (median), in 20% (3/15) of patients with two to three times weekly 30 IU/kg and in 25% with on demand treatment (tab. 2). Eleven (44%) out of 25 patients receiving prophylaxis with rFVIIII developed an inhibitor (table. 3). Contrastingly, only in 1 (5%) out of 20 pts treated prophylactically with pd FVIII an inhibitor was detected. ITI was performed in 7 out of 8 patients with a high titer inhibitor and was successful in 5. For ITI mainly pdFVIII products were used (5/7); 3 pts were switched during ITI from rFVIII to a pdVWF-containing FVIII product (tab. 4).

Tab. 2: Inhibitor formation and treatment regimen

	prophylaxis 2-3x/week 30 IU/kg	number of inhibitor patients	prophylaxis 1x/week 25 IU/kg	number of inhibitor patients	on de-mand	number of inhibitor patients
severe	15	**3 (20%) 2 HR/1 LR**	30	**9 (30%) 5 HR/4 LR**	4	**1 (25%) 1 HR**
moderate	1	0	2	0	3	0
mild	1	0	0	0	23	0
sub	0	0	0	0	13	0

HR – high responders; LR – low responders

Tab. 3: Characteristics of severe HA patients with prophylaxis

		without inhibitor (n=33; 73%)	with inhibitor (n=12; 27%)
age at start of prophylaxis (months)	median range	15 5 - 48	11.5 4 - 26
body weight-related dose at start of prophylaxis (1x/week)	median range	25 20 - 50 (n=19)	25 20 - 40 (n=9)
body weight-related dose at start of prophylaxis (2-3x/week) range	median	28 22 - 50 (n=13)	22 20 - 25 (n=3)
type of FVIII concentrate recombinant	plasma-derived	**19** **14**	**1** **11**
FVIII gene mutation	high risk low risk	22 11	11 1

Tab. 4: Characteristics of all inhibitor patients

		high titer (n=8)	low titer (n=5)	total (n=13)
age (months) at time of start of prophylaxis	median range	12 9 – 26	10 4 - 17	11.5 4 - 26
body weight-related dose at start of prophylaxis (1x/week)	median range	25 20 - 30	25 20 - 40	25 20 - 40
number of exposure days until inhibitor formation	median range	14 5 - 41	32 21 - 60	23 5 - 60
danger signals for inhibitor formation	yes no	3 (OP,Vac.) 5	3 (bleeding) 2	6 7
maximal inhibitor titer	median range	12 6 - >200	1,8 1,06 – 2,9	
performing ITI	yes (success) no (success)	7 (5) 1 (1)	0 5 (5)	
type of FVIII concentrate for ITI	recombinant FVIII pd FVIII pd VWF-FVIII recombinant → VWF-FVIII	2 1 1 3		

Conclusion

Our retrospective data did not confirm a lower inhibitor rate in PUPs with severe HA starting prophylaxis once weekly with low dose FVIII. This project is ongoing to extend the number of patients. However, prospective data are needed for a clear assessment of potential benefits of this new prophylaxis regimen.

References

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