The results of late immune tolerance induction in children with severe hemophilia A and inhibitor in Poland

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Introduction and Objectives:

The development of factor VIII inhibitors (FVIII) is the most serious complication in patients with haemophilia today. First-line treatment for patients with haemophilia A and inhibitors is to attempt to induce immune tolerance (ITI) by regular infusion of FVIII. The results of ITI are better when the procedure is started no later than 2 years after inhibitor detection. Complete success was noted in 72% of our young boys with haemophilia and inhibitors. The results of late immune tolerance induction (ITI) were presented in this study.

Materials and Methods:

In 2008 – 2012 ITI were used in 5 children with severe hemophilia A and FVIII inhibitor in Poland. Four boys were high-responders and one low-responder but without good response for factor VIII concentrates. Inhibitors were measured according to Bethesda method in Nijmegen modification.

Results:

The median age of patients was 9 years (ranged from 14 months to 10 years) in the time of inhibitor detection. Median of maximal titer of FVIII inhibitors found before ITI start was 20 BU/ml and ranged from 2,48 to 68 BU/ml. Immune tolerance induction was started in patients with median age of 13 years (ranged from 10 to 16 years). Titers of FVIII inhibitors ranged from 0,64 to 11,2 BU/ml (median 7,12 BU/ml) at the initiation of ITI regimen. All patients were treated with plasma derived FVIII concentrates, medium or high-purity. In 4 children ITI was started with single daily dose of ≥100 IU/kg, in 1 boy FVIII concentrate in a dose of 100 IU/kg was administered twice a day. Total elimination of factor VIII inhibitor was achieved in 3 patients. In the other 2 patients the ITI was failed and ITI regimen was discontinued after 14 months and 4 years. Duration of ITI ranged from 1 to 4 years (median 16 months). In patients with positive results the median duration of ITI was also 16 months (ranged from 12 to 18 months). In one boy Rituximab was added to the procedure of ITI with transient success and finally ITI was finished after 4 years. After achievement of complete ITI FVIII concentrates were infused 3 times a week in dose of 25 – 40 IU/kg prophylactically.

Conclusion:

The delayed introduction of ITI may be successful in children with severe haemophilia A. Despite better results of early introduced ITI there is a chance to total elimination of inhibitor in older children with longer-lasting inhibitors.

Table1. The course of late ITI in children with haemophilia A and inhibitor

Patient	Inhibior detection-patient age (years)	Max. Inhibitor level before ITI (BU)	Age of ITI start	ITI start - inhibitor level	ITI duration months	Dose of FVIII conc.	Max. inhibitor level during ITI	ITI results	Other drugs
PM	5	33	16	9	18	100U/kg every 24 h	4,8	Pos.	no
AP	1year 3 months	68	10	1,85	48	100U/kg every 12 h	22,80	Neg.	Rytuximab
PT	8	20	12	11,2	14	100U/kg every 24 h	64	Neg.	no
AK	11	10	13	7,12	16	100U/kg every24 h- 1 month, then every other day	1,2	Pos.	no
MW	10	2,48	14	0,64	12	100U/kg every24 h- 1 month, then every other day	0,74	Pos.	no