Low incidence of FVIII inhibitors in patients treated with plasma derived FVIII concentrates and the outcomes of immune tolerance induction with FVIII/vWF concentrates

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BACKGROUND

- The growing incidence of inhibitors in parallel with an increasing use of highly purified and recombinant FVIII preparations led to intensive study of the role of treatment products in this phenomenon.
- Most recently Gouw et al (NEJM 2013) demonstrated the cumulative incidence of clinically relevant inhibitors in 33.1% (high titer inhibitors 25.7%) of patients treated with pdFVIII, the frequency similar to that, observed after rFVIII products.
- However, the published data contrast with our clinical experience with pdFVIII concentrates, which are still predominantly used in our hemophilia population with a low incidence of inhibitors.

AIM

- To evaluate cumulative inhibitor incidence in all severe hemophilia A patients born 1997 - 2012, followed in two Hemophilia Comprehensive Care Centers (HCCC) in Slovakia.
- To evaluate the outcomes of the immune tolerance induction (ITI) in patients who developed inhibitor in a given period.

PATIENTS

Since 1997 all severe hemophilia A pats (FVIII <1 IU/dL) were systematically followed for inhibitor.
Inhibitor was evaluated in 51 pts who achieved at least >15 ED; 36 pts had >100 ED.

METHODS

TREATMENT PRODUCTS
- pdFVIII
- rFVIII – introdueced in 2007

INHIBITOR TESTING
- Bethesda method and Nijmegen modification
- Inhibitors above 0.7 BU or 0.5 Nijmegen BU confirmed by three consecutive tests were considered positive

INTERVALS OF INHIBITOR TESTING:
- Every 3-5, 10, 20 ED until a total of 20, 50 and 100 ED, respectively, than every 1/2 yr

IMMUNE TOLERANCE INDUCTION (ITI)
- So far 9/10 inhibitor pts. received ITI with FVIII/vWF concentrate employing a high dose (HD ITI) Bonn protocol for the high responders and a low dose (LD ITI) for the low titre inhibitors.

RESULTS

Tab 1. Characteristics of 41 patients undergoing joints replacement surgery between 1993-2013

Patients	Joints / Patients
No of joint replacements / No of pts.	58 / 41
Hemophilia A (No. Of surgeries / No.of pats)	38 / 27
Hemophilia B	2 / 2
Von Willebrand disease	5 / 5
Congenital Factor VII deficiency	13 /7
Median age at joint replacement	50 (30 – 60)
Follow up > 2 yrs (joints / patients)	50 / 33
Years of follow up (median, range)	6 (1,2-20)

Fig 1. FVIII products used in 51 hemophilia A patients

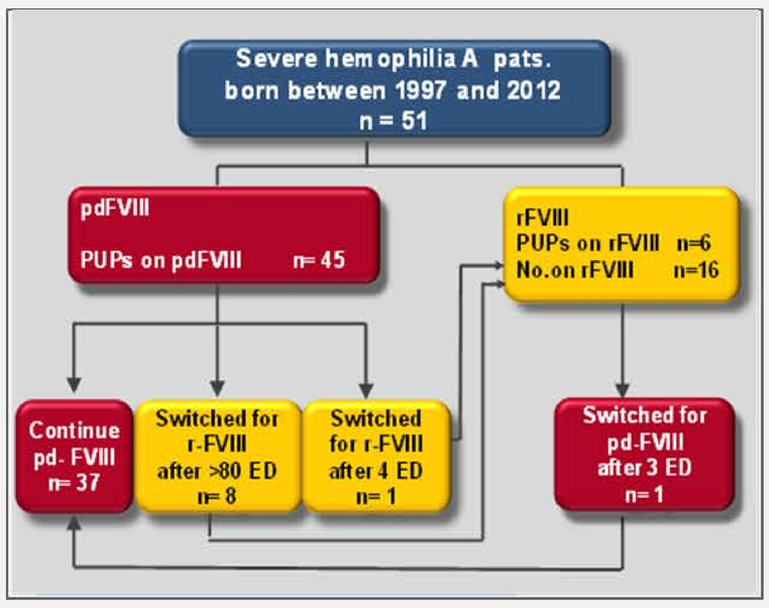


Fig 2. Cumulative incidence of inhibitors in 51 patients born between 1997-2013

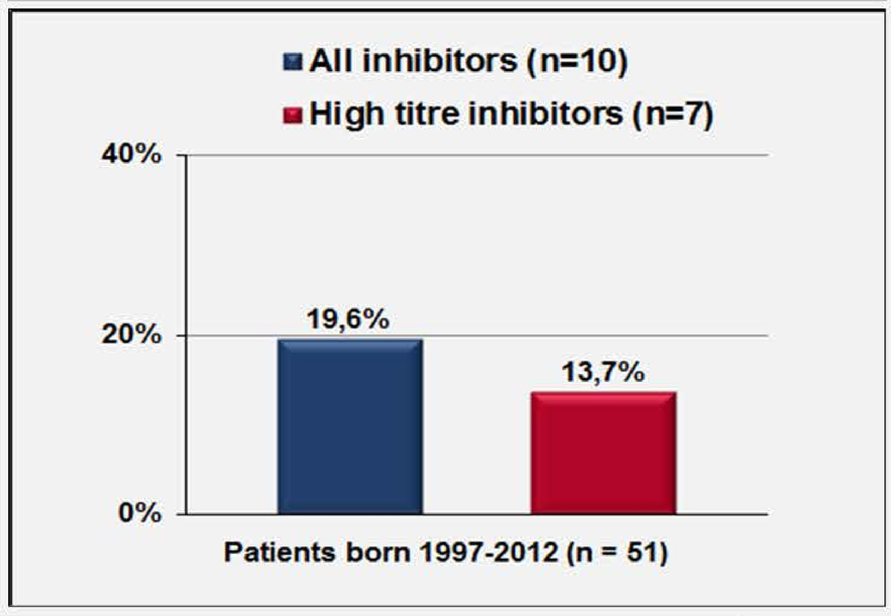
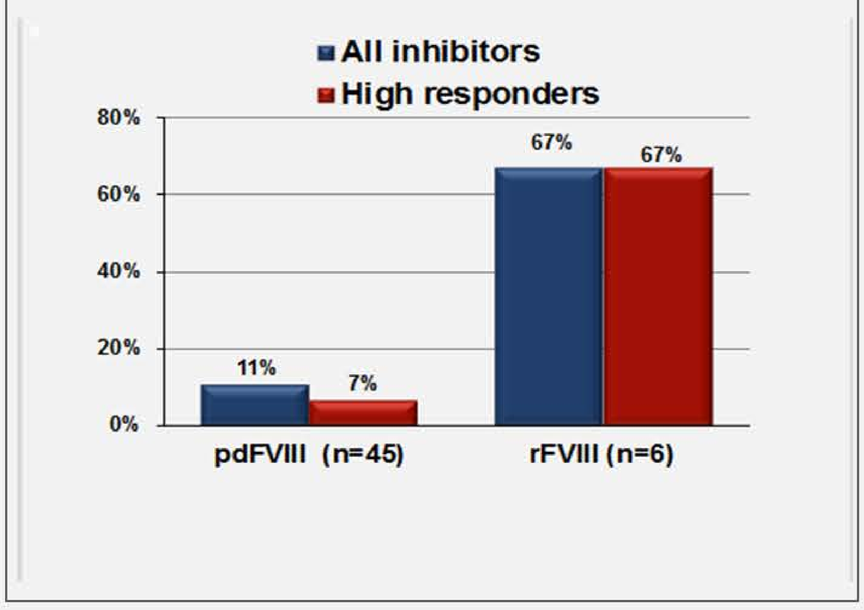


Fig 3. Inhibitors in PUP´s treated with pdFVIII (n= 45) and rFVIII (n=6)



Tab 2. Patients with inhibitor- and the outcome of ITI

P	Born	Age at inh mths	FVIII	ED (n)	Peak Tx ≥5 days	Inh titre at dg (BU)	Hist. peak (BU)	ITI regimen	ITI (mths)	Outcome
1	1997	60	pdFVIII	27	Yes	32	400	HD	19	Success
2	1998	60	pdFVIII	25	No	1,8	2.9	LD	6	Success
3	2000	17	pdFVIII	15	Yes	1,8	2.3	HD	8	Success
4	2006	24	pdFVIII	35	Yes	12	70	HD	12	Success
5	2007	24	pdFVIII	20	No	5,4	15	HD	9	Success
6	2008	11	pd➔rFVIII	25	No	1,4	1,9	LD	8	Success
7	2010	18	rFVIII	40	Yes	8,4	50	HD	24 +	ongoing
8	2011	14	rFVIII	20	No	5,4	35	HD	9	Success
9	2012	13	rFVIII	15	Yes	50	500	HD	in plan	waiting
10	2012	14	rFVIII	15	No	5,2	6,4	HD	1+	ongoing

LD: low dose (Dutch), HD: High dose (Bonn) regimen

CONCLUSIONS

- Cumulative incidence of inhibitors in 45 PUPs born between 1997-2012 and treated with pdFVIII was 5/11% (high titer 3/7%), much lower than that reported by Gouw et al (NEJM 2013) and similar to observation of Klukowska et al (Haemophilia 2013).
- Inhibitor developed one patient who switched from pdFVIII after 4 ED for rFVIII (21ED of rFVIII prior to inhibitor development).
- None of 8 patients who switched for rFVIII after >80 ED of pdFVIII developed inhibitor.
- Despite a small pts. group, a high incidence of high titre inhibitors (4/6; 67%) in our PUP´s treated with r-FVIII, is susrprising.
- We achieved a high rate of ITI success with FVIII/vWF, however, the management of inhibitor pts. is extremely demanding.

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