Czech National Haemophilia Programme

Use of rFVIII in PUPs is not associated with increased inhibitor incidence – Czech experience

PO090

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Introduction

Treatment with factor concentrates, including their use for bleeding prophylaxis, is the gold standard of care for persons with haemophilia (PWH) [1]. To date, both plasma-derived (pdFVIII) and recombinant (rFVIII) concentrates are available for the treatment of haemophilia A in the Czech Republic. All pdFVIII currently used are highly purified and since the introduction of pdFVIII in late 1990s there has never been any transmission of infectious disease recorded in relation with haemophilia treatment in the country.

Since 2003 Czech PWHs have also been treated with rFVIII and the proportion of those treated with recombinants has been constantly increasing. Children with severe haemophilia A are currently treated with primary prophylaxis. Low dose, escalation regimens close to "Canadian" [2] or "Bremen/Munich" regimen [3] are used in most of our haemophilia centres.

For more than 15 years systematic data records related to the diagnosis, treatment and its outcome have been collected on all children (age 0–18 years) with haemophilia in Czech Republic. These data then became a part of the Czech National Haemophilia Programme registry established in 2006. As all PUPs commenced on rFVIII since its launch in CZ have been children, we have detailed and representative data on all Czech PUPs with haemophilia, who have ever been treated with rFVIII to date.

Patients and methods

Data used for further analyses were extracted from the CNHP registry. We used records entered between 2003–2012. The CNHP registry is based on a modified version of TrialDB [4], which is fully compatible with systems used for collecting data from clinical trials and which complies with the strict criteria defined by ISO/IEC 20000-1:2006 and ISO/IEC 27001:2006. The database is accessible through on-line application via web browser. When the patient is registered, diagnosis, laboratory tests, presence of infectious diseases, etc. are recorded. Moreover, annual report on each patient is filled in each year – including the number of bleeds and their location, treatment (home treatment, prophylaxis/on-demand), type of administered factor concentrates and their consumption, development of inhibitors etc.

The incidence of inhibitor was calculated as absolute and relative. Absolute (cumulative) incidence reflects the proportion of patients with newly developed inhibitors in the cohort during the whole period. Relative (annual) incidence was calculated as a number of patients with newly developed inhibitor divided by the total number of treatment-years. It shows the percentage of newly developed inhibitors per year. Treatment-years at risk were calculated for each patient as the number of years in which the patient received rFVIII (or pdFVIII) until the inhibitor development or until the year 2012. Comparison of incidences was assessed by two-sample binomial test.

Table 1. Number of persons with haemophilia in the CNHP registry by the end of 2012

	No of persons	Of them with haemophilia A	Mild	Moderate	Severe	PUPs on rFVIII	PUPs on pdFVIII
Children	**233**	204	89	40	75	41	48
Adults	**411**	358	159	39	153		
Total	**644**	562	248	79	228		

Table 2. PUPs treated only with rFVIII within the CNHP registry

Severity of haemophilia A	No. of PUPs on rFVIII	No. (%) on prophylaxis	Of them on primary prophylaxis	No of treatment-years	Age in years (median)	No (%) of treatment-years on prophylaxis	No of PUPs with inhibitor
Mild	**11**	0 (0%)	0	**14**	7.5	0 (0%)	0
Moderate	**10**	1 (10%)	0	**28**	4	2 (7.1%)	0
Severe	**20**	16 (80%)	10	**76**	3	42 (55.3%)	4
Total	**41**	17 (41.5%)	10	**118**	3	44 (37.3%)	4

Table 3. Treatment outcomes (annual bleeding rates) in PUPs with haemophilia A treated with rFVIIIin the Czech Republic in 2003–2012

		Severity of haemophilia A			
		Mild	Moderate	Severe	Total
No of treatment-years	total	13	27	68	108
	on / without prophylaxis	0 / 13	2 / 25	40 / 28	42 / 66
Annual bleeding rate Mean	all bleeds	1.1	4.1	11.6	8.5
	on / without prophylaxis	- / 1.1	2.5 / 4.2	9.1 / 15.2	8.8 / 8.2
	joint bleeds	*- / 0.2*	*1.5 / 1.6*	*5.5 / 6.9*	*5.2 / 3.7*
	other bleeds	*- / 0.9*	*1 / 2.7*	*3.9 / 8.8*	*3.7 / 5*
Annual bleeding rate Median (min–max)	all bleeds	1 (0–2)	2 (0–19)	**6** (0–45)	4 (0–45)
	on / without prophylaxis	- / 1 (0–2)	2.5 (1–4) / 2 (0–19)	**5** (0–45) / **9.5** (1–44)	5 (0–45) / 3 (0–44)
	joint bleeds	*- / 0 (0–1)*	*1.5 (0–3) / 1 (0–12)*	***1*** *(0–32) /* ***3*** *(0–39)*	*1 (0–32) / 1 (0–39)*
	other bleeds	*- / 1 (0–2)*	*1 / 1.5 (0–9)*	***3*** *(0–16) /* ***5*** *(0–26)*	*2.5 (0–16) / 2 (0–26)*
Total bleeding rate	all bleeds	14	110	790	914
	on / without prophylaxis	- / 14	5 / 105	365 / 425	370 / 544
	joint bleeds	*- / 2*	*3 / 39*	*214 / 186*	*216 / 227*
	other bleeds	*- / 10*	*2 / 65*	*151 / 238*	*153 / 313*

Annual bleeding rate is missing for 10 treatment-years.
Location of bleed is unknown in 4 records without prophylaxis.

Table 4. Incidence of newly developed inhibitors against FVIII in PUPs with severe haemophilia A

	No of PUPs	No of treatment-years	No of PUPs with inhibitor	No of HR/LR	No of inhibitors developed on / without prophylaxis
rFVIII	20	76	**4**	2/2	1/3
annual incidence			**5.2%**	2.6% / 2.6%	2.4% / 8.8% (p = 0.211)
absolute incidence			**20.0%**	10% / 10%	7.1% / 50% **(p = 0.028)**
pdFVIII	23	128	**6**	6/0	1/5
annual incidence			**4.7%**	4.7% / 0%	1.4% / 9.3% **(p = 0.037)**
absolute incidence			**26.1%**	26.1% / 0%	9.1% / 41.7% (p = 0.076)

Results

By the end of 2012, 644 PWHs have been recorded into CNHP registry; 233 of them were children below 18 years of age. Eighty-nine of them were PUPs. Their data were used for the analyses performed within this study (Table 1).

Forty-one (46%) children with haemophilia A (20 of them with severe form of the disease) were treated only with rFVIII for 118 treatment-years (76 treatment-years in severe haemophilia A children). Ten children (24.3%) were commenced on primary and 7 (17.1%) on secondary prophylaxis. All PUPs on prophylaxis had the phenotype of severe haemophilia. Four children with severe haemophilia A and 20 with moderate or mild form of the disease had not the long-term prophylactic treatment (Table 2).

Regimen used for primary prophylaxis within the first 100 exposure days (ED) of rFVIII was 250 IU once per week with subsequent escalation to either 2 × 250 IU or 1 × 500 IU rFVIII per week. Regimens used for secondary prophylaxis during the first 100 ED were 1 × 750, 2 × 750 or 3 × 500 IU per week. In case of break-through bleeds, the dose and/or frequency was further escalated. After 100 ED the vast majority of children were treated with standard prophylaxis regimen of 20–50 IU/kg of rFVIII twice to three times per week.

On the treatment described above, the median total bleeding rate in children with severe haemophilia A on prophylaxis with rFVIII was 5 per year; in those without prophylaxis 9.5 per year. Joint bleeds appeared once per year on prophylaxis and three times per year without prophylaxis. Other bleeds had frequency of 3 and 5 per year in those on and without prophylaxis, respectively (Fig. 1). For further details see Table 3.

During the follow-up period, the relative incidence of inhibitors against FVIII in PUPs with severe haemophilia treated with recombinant concentrates only was 5.2% (4 PUPs during 76 treatment-years). Absolute incidence was 20% (4 out of 20 PUPs). Three boys developed inhibitors during first 20 ED, one during 50 ED. No inhibitor developed after 50 ED. None of the previously treated patients (PTPs), who were commenced on rFVIII during the follow-up period, developed inhibitors. No inhibitors developed in children with mild/moderate disease.

In PUPs with severe haemophilia A treated with pdFVIII only we found inhibitors in 6 patients during 128 treatment-years (relative incidence 4.7%; absolute incidence 26.1% , i.e., 6 of 23 PUPs). All of them appeared during first 50 ED. No inhibitors developed in children with mild/moderate disease. The difference between relative inhibitor incidence rate in PUPs treated with rFVIII and pdFVIII was not statistically significant (p = 0.873), see Fig. 2.

All inhibitors that developed against pdFVIII were high responding (HR), though in PUPs treated with rFVIII there were only 2 HR. Thus the annual incidence rate for HR inhibitors in PUPs treated with rFVIII was only 2.6%; absolute incidence was 10%.

When comparing relative (annual) incidence of inhibitors in PUPs with and without prophylaxis, we found that in both groups (pdFVIII and rFVIII treated PUPs) the incidence is lower in those, who were on the prophylaxis. This difference was statistically significant in our cohort (see Table 4.)

Fig. 1. Comparison of annual bleeding rates according to prophylaxis in PUPs with severe haemophilia A

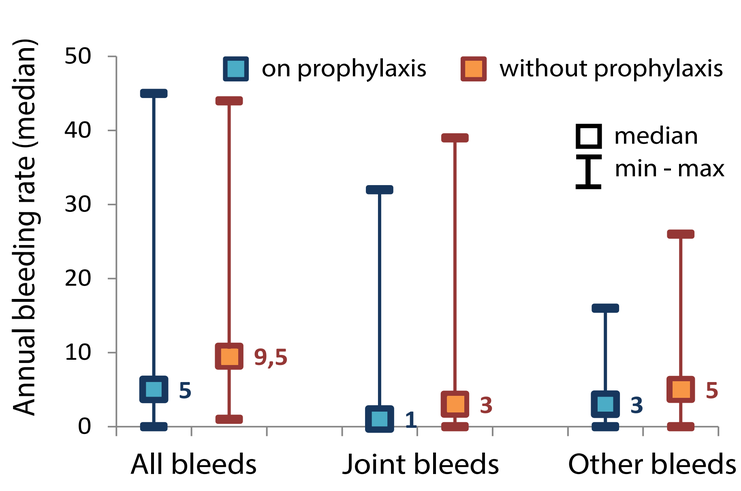
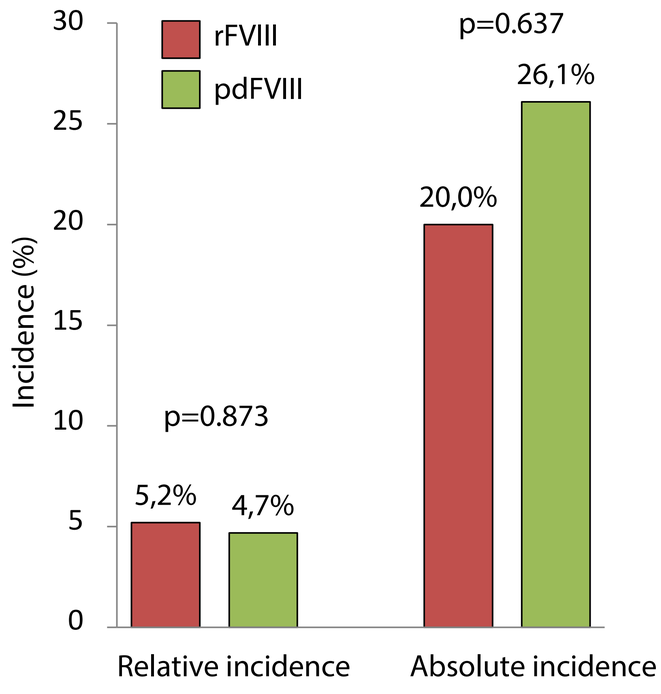


Fig. 2. Comparison of inhibitor incidence rates in PUPs with severe haemophilia A treated with rFVIII and pdFVIII



Discussion

Our results correspond with the finding that the use of recombinant products in PUPs with haemophilia does not increase the risk of inhibitor development [5]. Czech data, showing 20% of absolute incidence of inhibitors in PUPs treated with rFVIII, are similar to the results of Japanese authors, who described 15% incidence rate for their cohort of patients [6]. Though, compared to other data showing absolute incidence around 30% [5,7], or relative incidence of 6.4% [8], the incidence of inhibitors against rFVIII seems to be lower in Czech PUPs. We are, however, aware of the fact, that this possible difference is neither significant nor proven. We will further continue in following up the Czech PUPs and focus on this interesting finding. It might be beneficial to compare similar data from other Central European Countries (CEC) with similar historical prospective and current ways of haemophilia treatment to get more representative results based on a larger cohort of patients.

We might speculate that possible lower incidence of inhibitors may be related not only to the use of prophylaxis (only 2 out of 10 inhibitors developed in PUPs on prophylaxis, which correlates with deemed protective effect of prophylaxis in PUPs with Haemophilia [9]), but also to the fact that we have seldom used the doses of FVIII over 50 IU/kg neither for prophylaxis, nor for treatment of the bleeds in general. Long-term average of the prophylaxis dose in children with haemophilia in CZ varies around 25 IU/kg.

Conclusions

Inhibitor incidence in PUPs with haemophilia A has been relatively low in the Czech Republic during past 10 years. We do not see significant difference in incidence rate between those who were treated with recombinant and plasma derived products. Thus, we did not prove that the use of rFVIII would pose an increased risk of inhibitors development in PUPs with haemophilia A within our cohort.

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INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

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