Introduction
Treatment factor concentrates, including their use for bleeding prophylaxis, is the gold standard of care for persons with haemophilia and is recommended as standard of care in the World Federation of Haemophilia (WFH) guidelines and in most national haemophilia treatment guidelines. 

Since 2003 Czech PWHs have been treated with rFVIII and the proportion of those treated with recombinants has been continuously increasing in the Czech Republic. Low molecular weight (LMW) factor concentrates are available as the treatment of haemophilia A in the Czech Republic. All rFVIII 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. 

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, which is fully compatible with systems used for collecting data from clinical trials and which complies with the strict criteria defined by EEO/ECO 2000-1:2006 and ISO 27001:2006. The database is accessible through on-line application via web browser. When the patient is registered, diagnostic, 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. Low molecular weight factor concentrates are available as the treatment of haemophilia in the Czech Republic. Data on the use of factor concentrates is collected mainly at the teaching hospitals in the Czech Republic and the primary care hospitals in Prague. Emetics and self-treated patients are not included. 

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.

Patients and methods

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

<table>
<thead>
<tr>
<th>Severity of haemophilia</th>
<th>No. of PUPs on rFVIII</th>
<th>No. of inhibitor developed on rFVIII</th>
<th>Relative Incidence (per 100 treatment-years)</th>
<th>Annual Incidence (per 1000 patient-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Moderate</td>
<td>17</td>
<td>1 (0.0%)</td>
<td>5.8%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Severe</td>
<td>20</td>
<td>10 (50%)</td>
<td>500%</td>
<td>20%</td>
</tr>
</tbody>
</table>

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

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

Incidence of newly developed inhibitors against FVIII per 1000 patient-years at risk. 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.

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 (34%) children with haemophilia A (20 of them with severe form of the disease) were treated only with rFVIII for 118 treatment-years (76 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)

Regimens used for primary prophylaxis in the first 100 exposure days (ED) of FVIII was 250 IU once per week with subsequent escalation to either 2 or 250 IU 1 to 500 IU per week with intervals of 3 months. All PUPs on prophylaxis secondary prophylaxis during the first 100 ED were treated once 500 IU Ed. No inhibitors developed after 50 ED. None of the previously treated patients (PWHs), who were commenced on rFVIII during the follow-up period, developed inhibitors. No inhibitors developed in children with moderate/mild disease

In PUPs with severe haemophilia A treated with FVIII only we found inhibitors in 6 patients during 128 treatment-years (relative incidence 4.7%, absolute incidence 26.1, 6.1, 5, 6, 6 and 6 per 1000 patient-years). 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 FVIII 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 FVIII there were only 2 HR. Thus the annual incidence rate for HR inhibitors in PUPs treated with pdFVIII was only 2.6%, whereas absolute incidence was 10%.

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

Discussion

Our results correspond with the finding that the use of recombinant products in PWHs with haemophilia does not increase the risk of inhibitor development [5]. Czech data, showing the percentage of absolute incidence results of Japanese of Anthony who described 15% incidence in those with the 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 FVIII seems to be lower in Czech PWHs. We are, however, aware of the fact that this difference is neither significant nor proven. We will further continue in following up the Czech PWHs and focus on this interesting finding. It might be beneficial to compare some similar data from other Central European Countries (CEC) with similar historical perspective 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 patients on prophylaxis) which correlates with deemed protective effect of prophylaxis in PWHs with Haemophilia [9], but also to the fact that we have seldom used the doses of 500 IU 150 kg/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 was 11.6 IU/kg/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 rates between those who were treated with recombinant and plasma and used products. This, we do not prove that the use of FVIII would pose increased risk of inhibitors development in PWHs with haemophilia A within our cohort.

References