Original data on inhibitor incidence in 253 PUPs with severe haemophilia A from the FranceCoag Network: first analysis of risk cofactors

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Objectives
A French prospective cohort of patients with haemophilia has been set up in France since 1994. All the haemophilia centres participate in this cohort identified as FranceCoag Network in 2003 and coordinated by the French Institute for Public Health Surveillance *. In this cohort a subgroup of Previously Untreated Patients (PUPs) has been specially designed in order to study the inhibitor incidence in severe haemophilia A and the long term effect of prophylaxis regimen.

Patients and methods
Inclusion of children is proposed to the parents as soon as the patient is registered in one of the 37 participating centres *. Genetic risk cofactors of inhibitor are recorded:
- F8 genotype and ethnicity,
- Family history of haemophilia and inhibitor.
A follow-up visit is requested every 3 months until 150 cumulative exposure days (CED). At each visit, results of all inhibitor screening assays and environmental risk cofactors are collected via an electronic form:
- Date of first infusion and CED,
- Type of products (and possible switches),
- Prophylaxis,
- Severe bleeding episodes,
- Surgical procedures.

Results
By May 9th 2008, 253 PUPs with severe haemophilia A (FVIII<1%) have been included in the cohort. Currently between 20 and 30 children are included each year (Fig. 1).

Some data related to the genetic cofactors remain to be monitored and definitely validated and are still missing. However the analysis of the available data shows that 35.3% of the patients carry the inversion on the intron 22 or 1 inversion mutation, 20.5% are non Caucasian and 9.5% have a family history of inhibitor (Table 1). Seventeen patients were still unexposed to FVIII and 236 were treated at least once. Among those, 19.9% received their first treatment before the age of 3 months, 16.6% received a plasma-derived FVIII (pdFVIII) as first treatment whereas 83.9% received a recombinant FVIII (rFVIII) concentrate (Table 1).

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- Surgical procedures.

**Table 1. Characteristics of the cohort.**

<table>
<thead>
<tr>
<th>Genetic cofactors</th>
<th>N</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inversion (intr 1 or 22)</td>
<td>158</td>
<td>83</td>
<td>(52.5)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>176</td>
<td>36</td>
<td>(20.5)</td>
</tr>
<tr>
<td>Family history of haemophilia</td>
<td>231</td>
<td>116</td>
<td>(50.2)</td>
</tr>
<tr>
<td>Family history of inhibitor</td>
<td>231</td>
<td>22</td>
<td>(9.5)</td>
</tr>
<tr>
<td>Environmental cofactors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first infusion &lt;3 months</td>
<td>236</td>
<td>47</td>
<td>(19.9)</td>
</tr>
<tr>
<td>Age at first infusion 3-11 months</td>
<td>236</td>
<td>107</td>
<td>(45.3)</td>
</tr>
<tr>
<td>Initial treatment pdFVIII</td>
<td>236</td>
<td>38</td>
<td>(16.1)</td>
</tr>
</tbody>
</table>

The median time to follow-up after inclusion in the cohort is 3.39 years (min-max: 0-13.11) and the total observation period is 970.5 person-year. The median exposure is 216 CEDs including 181 CEDs with the same FVIII type as the initial treatment. 169 children have at least 50 CEDs with the same FVIII type received as initial treatment (pdFVIII in 19 and rFVIII in 150) whereas 14 received at least one injection of the other FVIII type before 50 CEDs (7 in the group of pdFVIII and 7 in the group of rFVIII as initial treatment).

As a whole 71 children (28.1%) developed an inhibitor (>0.6 BU) including 35 (13.8%) with a high titer inhibitor (>5 BU). The median exposure at inhibitor detection is 14 CEDs (min-max: 3-122). In most of the cases (95.5%) the inhibitor was detected before 50 CEDs.

The cumulative incidence at 50 CEDs is 31.0% (95%CI: 25.2-37.9) for all inhibitors and 16.6% (12.0-22.7) for high titer inhibitors (Fig. 2).

**Figure 2.** Kaplan-Meier curves of survival without all inhibitors (—) and without high titer inhibitors (—).

**Conclusion**
These results have to be considered as preliminary data on the French cohort of PUPs with severe haemophilia A. The effect of the genetic and environmental cofactors will be further analysed as far as the complete data on each patients will be available. Several prospective PUPs cohorts studies are currently in progress in different countries. The comparison of their results can help to (1) refine knowledge about inhibitor risk factors that could lead the clinicians to adapt the treatment regimen and (2) suggest physiopathological hypothesis opening new perspectives of research.

* FranceCoag Network participants are listed in general presentation poster:
Chambost et al. FranceCoag Network: a national multicenter prospective cohort for congenital bleeding disorders