Implementation of national recommendations of early prophylaxis in boys with severe hemophilia: results from the PUPS Cohort of “FranceCoag Network”

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Rationale

During the last decades, long term prophylaxis (LTP) has become the gold standard treatment of children with severe hemophilia A (HA) and B (HB). In 2002, the French society MEDical COordination for Hemophilia Treatment (CoMETH) promoted recommendations of early LTP in severe hemophilia¹. In a national study sponsored by the Ministry of Health in the framework of the program for Hospital Clinical Research, we aim to analyze comprehensively the implementation of these recommendations. The main objectives were to check the feasibility of such a national program and to identify factors that may influence the adherence.

This study is connected to the PUPS Cohort (PC) that has been designated within the FranceCoag Network project to pursue specific research purposes including the impact study of standardized prophylaxis regimen in severe hemophilia.

Design of French Recommendations¹

The specific guidelines entitled “Early long term prophylaxis with escalating intensification in severe hemophilia A and B” are dedicated to children with severe HA or HB, aged 3 years or less, with no history of target joint or arthropathy.

Criteria for starting with this LTP regimen:
- Not later than after the 2nd hemarthrosis in one or two major joints (ankle, knee, elbow) during a 6 month period,
- or after the third hemarthrosis whatever the joint,
- and with clinically normal joints (no sign of arthropathy).

➔ 4 step escalating dose PLD schedule for HA²

<table>
<thead>
<tr>
<th>Step</th>
<th>Dose FVIII</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30 UI/kg</td>
<td>once weekly</td>
</tr>
<tr>
<td>2</td>
<td>30 UI/kg</td>
<td>twice weekly</td>
</tr>
<tr>
<td>3</td>
<td>30 UI/kg *</td>
<td>thrice weekly or every 3 days</td>
</tr>
<tr>
<td>4</td>
<td>25 à 30 UI/kg *</td>
<td>alternate days</td>
</tr>
</tbody>
</table>

* Adjustment to trough level in case of inefficiency

** a specific schedule of treatment was adapted for HB patients

Criteria for escalating

A non-tolerant adaptation is recommended with an escalation to the further step from the occurrence of the first “spontaneous” or second post-trauma joint bleeding.

Inclusion criteria

All the boys with HA or HB included in the FranceCoag PUPS Cohort (FVIII/FIX level < 2%) and born in the [2000-2007] period are eligible for the study.

Exclusion criteria:
- Girls
- Patients treated in centers of overseas departments who did not participate immediately in the FranceCoag Network project
- Patients with HB Leiden
- Patients born before 2000 or after 2007

Patients/Methods

At the date of analyses (November 29th, 2011), all the eligible patients were at least 3 years old, that was mandatory to reach the main endpoint.

All the data presented are focused on the first 3 years of life and restricted to the boys with severe HA to get homogeneous results on the most important group of patients. Incompletely informed files, particularly as regards the description of bleedings and treatments, were excluded.

Patients who may not have been eligible for the recommendation because of a concurrent event, i.e. intracranial bleeding, inhibitor or death, before they experienced the first joint bleeding or before they started PLD and before the age of 3 years were excluded.

Results

First Hemarthrosis

140 patients (65.7%) experienced at least 1 joint bleeding (JB)

The first hemarthrosis occurred at the median age of 1.5 years (Interquartile Range / IQR: 1.0-2.2 y)

Start of LTP

110 patients (51.6%) started a LTP regimen before 3 years in the cohort at the median age of 1.8 years (IQR: 1.3-3.3)

Joint bleeding before LTP

Among these patients, 28.2% started before any JB, 35.5% after the 1st and 20% after the 2nd joint bleedings. 93.6% started before the 4th JB.

Hemarthrosis in patients still treated on demand by 3y

Among these 103 boys, 50 (48.5%) did not experience any JB at 3y, 25 and 12 had 1 or 2 JB, respectively. i.e. 84.5% had less than 3 JB

Conclusions/Perspectives

"CoMETH" recommendations of early LTP have had a major impact on clinical practice in France as suggested by the correlation of age at start of LTP and age at the occurrence of the first joint bleedings. The escalating pattern with a weekly first step appears as a reasonable option.

Further results will be helpful to identify factors that may be related to adhesion.


