Dear Sirs,

Considering the high quality of replacement therapy available nowadays for haemophiliacs, the most challenging complication of haemophilia is currently the development of inhibitors, which render replacement therapy ineffective, preclude the access of patients to a safe and effective standard of care (particularly prophylaxis in children) and predispose them to a high risk of morbidity and mortality, causing moreover striking increases in healthcare costs (1–5). Although the development of activated prothrombin complex concentrate (aPCC) FEIBA first and then of recombinant activated FVII (rFVIIa) NovoSeven has dramatically improved the management of acute bleeding in patients with haemophilia complicated by inhibitory alloantibodies (6), it should, however, be recognised that both bypassing agents have lesser efficacy in the prevention and treatment of bleeding episodes in inhibitor patients, than replacement therapy with clotting factor concentrates in non-inhibitor ones (7).

Alloantibodies that neutralise factor replacement therapy develop in approximately 25–30% of patients with severe haemophilia A, while an inhibitor incidence of 1–5% is reported in patients with severe haemophilia B (1, 8, 9). In spite of lower incidence, inhibitors in haemophilia B show the additional morbidity issues of allergic up to severe, even life-threatening, anaphylactic reactions, reported in approximately 60% of cases (4). However, while inhibitor incidence and related risk factors have been extensively studied for haemophilia A, little is known about the true incidence of inhibitors in severely affected haemophilia B patients, probably due to the rarity of this inherited bleeding disorder. Notably, the great majority of studies or registries published so far report the overall prevalence of inhibitors in the cohorts of evaluated patients with haemophilia B, but do not clearly differentiate them on the basis of the disease severity (i.e. severe, moderate or mild haemophilia B), or between previously treated or untreated patients (PTPs or PUPs), or analyse the relationship between product type (i.e. plasma-derived vs recombinant Factor IX [FIX] concentrates) and the inhibitor risk. These aspects are, however, not insignificant considering that they have been consistently found to be strongly implicated in the development of inhibitors in haemophilia A patients (9). Thus, in order to elucidate these still unclear issues, we have conducted for the first time a systematic review of the existing literature on inhibitor development in severe haemophilia B (i.e. FIX <1%) PUPs, who represent the most suitable model for studying this phenomenon.

A computer-assisted search of the MEDLINE and SCOPUS electronic databases without time limits was conducted using different combinations of the following keywords: “haemophilia B”, “severe congenital factor IX deficiency” “inhibitor”, “alloantibody”, “previously untreated patients”, “anaphylaxis”, “factor IX concentrates”, “recombinant factor IX products”. A specific electronic search was also performed using the commercial names of licensed FIX products reported in the World Federation of Haemophilia (WFH) Registry of clotting factor concentrates (10). In addition, the reference lists of all included studies were manually searched for other potentially eligible studies. Moreover, we supplemented our search by reviewing abstract books of the most important conferences on haematological diseases.

Overall, 374 studies were initially retrieved and 331 were excluded as focusing on other topics or because they were review articles. Thus, 33 potentially relevant clinical reports were identified and examined in detail. Of them, 26 were further excluded because the relevant data were unavailable, or because analysed patients were included in other published studies or because the design of the study did not permit a pooled analysis of the data. Finally, seven studies with usable information (6 prospective, 1 retrospective/prospective), published between 1996 and 2015, were included in this systematic review (11–17), as reported in Table 1. Statistical analysis was performed using the Chi-square test or the Fisher’s Exact test, as appropriate. A p-value less than 0.05 was considered statistically significant.

Overall, 176 severe haemophilia B PUPs were reported in the included studies: 85 were treated with plasma-derived FIX concentrates and 91 with recombinant FIX products. Inhibitor rates between 5% and 14% were found, with an outlier value of 37% in a Swedish study, consistent with previous data, probably due to the genetic background (18). Overall, inhibitors occurred in 18 patients (10.2%). When the type of concentrate was considered, no data were available in a study reporting two inhibitor patients (15), whereas the other six studies provided a statistically significant higher inhibitor rate in patients treated with plasma-derived versus recombinant FIX products (11/72 [15.3%] vs 5/89 [5.6%], p=0.04). Among the 18 cases of inhibitors, seven were high responding and six low responding; in the remaining five patients, inhibitor titres were not reported. In the majority of cases with available information, inhibitors were associated with anaphylaxis (4/5, 80%). Finally, a
high risk mutation was found in 73% (8/11) of the inhibitor patients (Table 1). A multivariate analysis was not possible due to the paucity of data reported.

Data from our systematic review confirm much of what is already known about inhibitors in haemophilia B. However, in spite of the relatively small number of evaluable patients, notably, the overall incidence of inhibitors detected in PUPs is consistently higher (about twice) than that historically reported, irrespective of the recognised higher rates in some populations (13, 18). An explanation of such discrepancy probably resides, as previously mentioned, in the fact that most registries or trials on haemophilia B did not differentiate between patients with a severe or moderate defect or between FIX concentrate unexposed or previously exposed patients. This important bias could have led to an underestimation of the real inhibitor risk in severe haemophilia B PUPs by previous epidemiological studies and reviews (4). Worthy of interest is also the observation of the increased rate of inhibitors in PUPs treated with plasma-derived versus those receiving recombinant FIX products (15.3 % vs 5.6 %), although the low number of events reported (i.e. inhibitor development) does not allow to make definitive conclusions or to implicate a particular type of FIX product. If confirmed by further studies, this finding could be, however, related to the peculiar anaphylactoid nature of most alloantibodies in haemophilia B (19), which could account for the increased immunogenicity of the former product. Finally, our systematic review confirms the key role of genetic factors in the inhibitor risk also in severe haemophilia B PUPs, as high risk F9 mutations (Table 1) were detected in more than 70 % of valuable informative inhibitor patients. This highlights the need for an early molecular diagnosis in children with severe haemophilia B, according to recent expert recommendations, in order to identify genetically higher-risk patients (4, 23).

Table 1: Characteristics and results of the studies included in the systematic review.

<table>
<thead>
<tr>
<th>First author, year [Ref]</th>
<th>Study design</th>
<th>SHB PUPs, n</th>
<th>FIX product</th>
<th>Inhibitors n (%)</th>
<th>HR(^1), n (% inh)</th>
<th>LR(^1), n (% inh)</th>
<th>Allergy/-anaphylaxis, n (% inh)</th>
<th>High-risk F9 mutations(^2), n (% inh)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shapiro, 1996 [11]</td>
<td>Prospective</td>
<td>11</td>
<td>pdfIX (Mononine)</td>
<td>1/11 (9)</td>
<td>1/1 (100)</td>
<td>0/1</td>
<td>1/1 (100)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Parquet, 1999 [12]</td>
<td>Retrospective/prospective</td>
<td>15</td>
<td>pdfIX (LFB)</td>
<td>1/15 (7)</td>
<td>1/1 (100)</td>
<td>0/1</td>
<td>0/1</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Knobe, 2002 [13]</td>
<td>Prospective</td>
<td>16</td>
<td>Intermediate/high-purity pdfIX</td>
<td>6/16 (37)</td>
<td>2/6 (25)</td>
<td>4/6 (75)</td>
<td>NR</td>
<td>4/6 (75)</td>
</tr>
<tr>
<td>Shapiro, 2005 [14]</td>
<td>Prospective</td>
<td>40</td>
<td>rFIX (BeneFIX)</td>
<td>2/40 (5)</td>
<td>2/2 (100)</td>
<td>0/2</td>
<td>2/2 (100)</td>
<td>1/2 (50)</td>
</tr>
<tr>
<td>Kreuz, 2005 [15] GTH</td>
<td>Prospective</td>
<td>15</td>
<td>13 pdFIX, 2 rFIX (BeneFIX)</td>
<td>2/15 (13)</td>
<td>1/2 (50)</td>
<td>1/2 (50)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Monahan, 2010 [16]</td>
<td>Prospective</td>
<td>7(^1)</td>
<td>rFIX (BeneFIX)</td>
<td>1/7 (14)</td>
<td>0/1</td>
<td>1/1</td>
<td>1/1 (100(^4))</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Fischer, 2015 [17] EUHASS</td>
<td>Prospective</td>
<td>72</td>
<td>30 pdFIX, 42 rFIX (BeneFIX)</td>
<td>5/72 (7)</td>
<td>3 (10) pdFIX</td>
<td>2 (5) rFIX</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>176</td>
<td>85 pdfIX, 91 rFIX</td>
<td>18/176 (10.2)</td>
<td>pdfIX: 11/72 (15.3)</td>
<td>rFIX: 5/89 (5.6)(^5)</td>
<td>7/13 (54)</td>
<td>6/13 (46)</td>
</tr>
</tbody>
</table>

Abbreviations: EUHASS, European HAemophilia Safety Surveillance; GTH, German, Swiss and Austrian Society of Thrombosis and Haemostasis Research; HR, high responders; LR, low responders; NR, not reported; pdfIX, plasma-derived factor IX concentrate; PUPs, previously untreated patients; rFIX, Recombinant factor IX concentrate; SHB, severe haemophilia B (FIX levels:<1 %). \(^1\)Historical peaks of anamnestic response of inhibitor levels up to 5 BU identified the so-called low responders, while peak inhibitor levels >5 BU identified the high responders. \(^2\)Null F9 mutations, i.e. complete/partial gene deletions, nonsense or frameshift mutations. \(^3\)Only PUPs and patients with <20 ED enrolled in this study were considered. \(^4\)This patient had only mild allergic reactions. \(^5\)Inhibitor incidence with pdfIX versus rFIX products was significantly different (p=0.04, Fisher’s Exact test).
In conclusion, our study suggests that, although inhibitors in severe haemophilia B PUPs are definitely more rare compared to haemophilia A, however they are likely to be less rare than previously thought, being reported in approximately 10% of patients. It should be stressed, however, that our results have to be considered preliminary and that ongoing and future studies and registries should address the incidence of inhibitors in PUPs with haemophilia B, focusing on a better stratification of patients according to disease severity and type of treatment, in order to further elucidate the still poorly understood issues of the inhibitor risk and the factor concentrate immunogenicity. These aspects will be particularly interesting for newer recombinant FIX concentrates with extended half-life, already on the market or licensed in few years (24), for which no data of inhibitor development in PUPs are currently available.

Conflicts of interest
None declared.

References

Erratum to Loboda et al. “Carbon monoxide: pro- or anti-angiogenic agent? Comment on Ahmad et al. (Thromb Haemost 2015; 113: 329–337)

In the Author Correspondence ”Carbon monoxide: pro- or anti-angiogenic agent? Comment on Ahmad et al. (Thromb Haemost 2015; 113: 329–337), the number of the second grant listed in the Acknowledgements contains a mistake. The correct statement is: “The authors’ research is supported by the grants from the National Science Centre (Maestro – No: No. 2012/06/A/NS1/00004; Opus – No. 2012/07/B/NS1/02881 and Harmonia – N N301 460938) and National Centre for Research and Development (PBS2/B7/15/2014).”

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