To the editor:

**Reflections on the FranceCoag report on inhibitory antibodies to factor VIII in patients with severe hemophilia A**

Calvez et al exhaustively reported their excellent analysis of the FranceCoag Database, showing a higher risk of inhibitors for Kogenate over Advate. Because they acknowledge the absence of a definitive biological rationale for their findings, we wish to suggest a possible explanation for their findings.

Calvez et al found that Kogenate was associated with an inhibitor rate of ~50% (1 in 2 patients). They also showed that this rate has not changed over time, which implies that this evidence has been available from their countrywide surveillance system for some time before their recent publication, which, as discussed in the paper, has been prompted by the unexpected results from the PedNet Registry. Although it is possible that the high inhibitor rate with Kogenate had gone unnoticed, a plausible alternative explanation is that such a high event rate was somehow anticipated, as a consequence of a selective use of Kogenate in patients at higher risk of inhibitor development. Indeed, imbalance in the baseline risk of events is the most common flaw in observational studies. To test this hypothesis, we provide an additional sensitivity analysis of the FranceCoag data and an explanation.

In supplemental Table 19 from Calvez et al, a breakdown by center of their database is provided. Only 3 centers contributed >10 patients on Kogenate or Advate and observed an inhibitor rate for Kogenate of >50%. In Table 1, we contrast pooled data from these 3 centers (ie, 1, 3, and 13 in their supplemental Table 19) with pooled data from the remaining 34 centers. The absolute difference in inhibitor rate between Kogenate and Advate was a clinically and statistically significant 41% (95% confidence interval [CI], 17% to 47%) for the 3 selected centers and a completely irrelevant 3% (95% CI, −11% to 18%) for all other centers (with a large sample size of 161 previously untreated patients [PUPs] and 56 inhibitors; overall rate, 34%).

From the participant list provided in Calvez et al, centers 1, 3, and 13 are Paris Necker, Lille, and Strasbourg. During the years between 1997 and 2001, Paris Necker and Lille provided data on Kogenate for a study published in 2005, claiming a very low inhibitor rate. We consider it reasonable to imagine that the 3 centers, based on their experience, had been keen to use Kogenate in high-risk patients with the hope of reducing their inhibitor risk and had not been surprised by observing a 60% inhibitor rate in 93 higher-risk patients. Correspondingly, the inhibitor rate in the patients treated with Advate in those 3 centers was 17%, which was significantly lower than the overall rate and very close to the 15% inhibitor rate reported by Kreuz et al for Kogenate.

Thus, a possible explanation is that with selection of Kogenate for higher-risk patients, the patients who remained for Advate were necessarily at lower risk of inhibitor development. In contrast, it is possible that all the other centers considered Kogenate or Advate as equivalent choices for their patients and thus did not introduce confounding by indication. Unfortunately, even the state-of-the-art multivariable analysis performed by Calvez et al cannot adjust for all the subtle nuances (including, but not limited to, low economic and education level, difficulty in vein access, expected low compliance, and their association with known risk factors for inhibitors) that constitute the expertise of those treating hemophilia in assessing the risk of inhibitors of their patients.

The most efficient option to address residual confounding would be to randomize 120 patients to Kogenate or Advate, ruling out a hazard ratio of ≥1.6 with a power of 80% and a 1-sided α of 0.05 and adjusting the analysis for known covariates. Is this feasible, ethical, and worthy? We invite the readers’ opinion via e-letters, and we prompt manufacturers to consider sponsoring such a trial.

Kessler and Iorio suggested that a center effect was not tested in Research of Determinants of Inhibitor Development (RODIN), but the authors ignored our criticism. We could test the center effect with the FranceCoag report, because of the more detailed reporting. We again urge the RODIN authors to report center-level data for their study. These data belong to the community and cannot be kept secret, leaving patients and those treating the patients with doubts as to whether they are receiving suboptimal treatment. Any rational clinical decision has to be made after considering the entire body of available evidence.

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**Table 1. Exploring the effect of center in the FrenchCoag database**

<table>
<thead>
<tr>
<th>Centers</th>
<th>Kogenate</th>
<th>Advate</th>
<th>Kogenate – Advate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (PUPs)</td>
<td>Inhibitors (%)</td>
<td>N (PUPs)</td>
</tr>
<tr>
<td>All centers</td>
<td>234</td>
<td>124</td>
<td>56</td>
</tr>
<tr>
<td>Centers 1, 3, and 13*</td>
<td>73</td>
<td>50</td>
<td>29</td>
</tr>
<tr>
<td>All centers except 1, 3, and 13</td>
<td>161</td>
<td>74</td>
<td>27</td>
</tr>
</tbody>
</table>

Absolute difference was calculated as percentage for Kogenate minus percentage for Advate. A positive value indicates a higher rate with Kogenate. 95% CI was calculated as suggested by Newcombe. When the interval does not cross 0, the difference is significant.

*Centers with >10 patients on Kogenate (product D) or Advate (product E) and inhibitor rate for Kogenate >50%.
Response

Confounding by indication is unlikely to explain the higher inhibitor incidence in boys treated with a recombinant FVIII product

In January 2013, the Research of Determinants of Inhibitor Development (RODIN) study unexpectedly showed a higher inhibitor incidence in previously untreated patients (PUPs) with severe hemophilia A treated with Kogenate FS (Bayer) (also named Helixate NexGen; Product D in this letter) than in those treated with Advate (Product E). Two other groups in charge of national hemophilia cohorts in the United Kingdom and France recently published similar findings. Given the lack of an obvious pathophysiologic mechanism, possible biases have been raised. One of the most plausible is confounding by indication (CbI), whereby Product D has been stable since market release, and (2) to determine whether production in baby hamster kidney cells is involved.

Berntorp and Iorio further discuss this possible bias, postulating that (1) this bias might have existed in only a few hemophilia treatment centers (HTCs), and (2) prescribers might have selected “at-risk” patients based on subtle nuances not recorded in cohort studies and therefore not considered in multivariate analyses. They analyzed our tabulated data, comparing inhibitor rates between Products D and E, first in 3 selected HTCs (in which at least 10 patients were treated first with Product D or E and where an inhibitor rate of at least 50% was observed with Product D), and then in the remaining 30 HTCs. We performed survival analyses in these 2 HTC groups, adjusted for the same risk factors as in our article. Adjusted hazard ratios (aHRs) for Product D compared with Product E (D/E) were 3.20 (95% confidence interval [CI], 0.93-11.0) for the first 3 HTCs and 1.23 (95% CI, 0.68-2.23) for the remaining 30 HTCs.

In the early 2000s, the only well-known risk factors for inhibitor development were genetic, namely, the F8 gene defect, a family history of inhibitors, and ethnic origin. If some prescribers had indeed preferred Product D for at-risk PUPs, an association should have emerged between these genetic risk factors (if known at the first factor VIII [FVIII] infusion) and the chosen product. However, no consistent trend has been found, either in the entire sample of the 3 published studies or in the aforementioned subgroups of French HTCs (Table 1). Furthermore, when a product is deemed less immunogenic (eg, plasma-derived FVIII products), its preferential prescription to at-risk patients is apparent (see RODIN results, Table 1). Some subtle nuances in socioeconomic conditions or practical modalities of initial treatment, as highlighted by Berntorp and Iorio, might correlate with inhibitor risk factors, but their independent association with inhibitor development remains to be demonstrated. Nevertheless, it would be rather odd for preferential product prescription to be based on such characteristics and not on acknowledged genetic risk factors.

The first article showing a low inhibitor rate with Product D included limited numbers of PUPs of white European origin and minimally treated patients (n = 31), followed until the 20th exposure day. Only 3 French HTCs (6 patients in total) participated in this study. The second article reported 30 additional American PUPs and had similar limitations. Because of these limitations, it could be considered that the observed inhibitor proportion (9/60) underestimated the real-life risk with Product D. The clinicians in charge of the 3 aforementioned French HTCs (J.G., P.L., and C.R.) certify that they never preferentially prescribed Product D to at-risk PUPs. Nevertheless, these clinicians and other French clinicians we interviewed stated that their product choice for PUPs was influenced by other factors, such as FVIII product shortages (eg, Product D production was reduced in 2001 after an inspection by the US Food and Drug Administration), their willingness to use various brands of FVIII products in their HTC, and practical considerations (eg, some clinicians preferentially chose Product D for children owing to its lower injected volume compared with Product E). The numbers of PUPs first treated with Products D and E per HTC show no discernible temporal pattern (supplemental Data, available on the Blood Web site).

Although the CbI hypothesis is unlikely, it cannot be formally excluded. To explore it further, we repeated our primary analysis after incorporating propensity scores (PS) based on inhibitor risk factors known at the first FVIII infusion (see characteristics shown for the FranceCoag Network, Table 1). Estimated D/E HRs obtained with a Cox model adjusted on PS were slightly lower than our published results: crude HR 1.59 (95% CI, 1.02-2.48) and aHR 1.46 (95% CI, 0.88-2.41). Although this statistical technique cannot consider unmeasured confounders, these preliminary results do not support a major CbI.

Given the heterogeneity of inhibitor rates observed with each product in the different HTCs (mainly because of limited patient numbers), a very broad spectrum of relative risk estimates can be obtained by selecting HTC subgroups. Without a clear demonstration of CbI, any calculation based on arbitrary HTC subgroups remains unconvincing.

We agree that a properly conducted randomized trial comparing Products D and E would provide stronger evidence of a difference in immunogenicity. Unfortunately, implementation of such ambitious comparative trials in PUPs appears difficult in Western countries. Another approach would be to identify a pathophysiologic mechanism for the suspected difference, and this is why we called for nonclinical studies. If a difference in immunogenicity exists, the 2 main issues would be (1) to assess whether the immunogenicity of Product D has been stable since market release, and (2) to determine whether production in baby hamster kidney cells is involved.

References

Reflections on the FranceCoag report on inhibitory antibodies to factor VIII in patients with severe hemophilia A

Erik Berntorp and Alfonso Iorio