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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).[1] Two other groups in charge of national hemophilia cohorts in the United Kingdom and France recently published similar findings.[2,3] Given the lack of an obvious pathophysiologic mechanism, possible biases have been raised.[1-5] One of the most plausible is confounding by indication (CbI),[6] whereby Product D might have been preferred for initial treatment of PUPs with a high a priori inhibitor risk, after publication of 2 articles reporting a low inhibitor rate with this product.[7,8]

Berntorp and Iorio further discuss this possible bias,[9] 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.[3] 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[1-3] 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).[1,5] Some subtle nuances in socioeconomic conditions or practical modalities of initial treatment, as highlighted by Berntorp and Iorio,[9] 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.[7] Only 3 French HTCs (6 patients in total) participated in this study. The second article reported 30 additional American PUPs and had similar limitations.[8] 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)[6,10] 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[3]: 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.[11] Another approach would be to identify a pathophysiologic mechanism for the suspected difference, and this is why we called for nonclinical studies.[3] 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.

Table 1. Patient characteristics according to the first factor VIII product received

Characteristics	Product E (Advate) N	%	Δ†	Product D (Kogenate FS) N	%	Δ†	Plasma-derived FVIII products N	%
RODIN study[1]*	157			183			88	
High-risk *F8* genotype	95	60.5	–	100	54.6	++	56	63.6
Family history of hemophilia and inhibitor	22	14.0	–	16	8.7	+++	20	22.7
Nonwhite race	20	12.7	-	16	8.7	-	7	8.0
History of peak treatment episode on first exposure day ≥3 d	40	25.5	-	41	22.4	+++	30	34.1
History of peak treatment episode on first exposure day ≥5 d	28	17.8	–	21	11.5	+++	24	27.3
UK Haemophilia Centre Doctors' Organisation[2]*	172			128				
High-risk FVIII mutation (including inversion)	103	59.9	-	71	55.5			
Family history of hemophilia and inhibitor	15	8.7	++	18	14.1			
Nonwhite ethnicity	25	14.5	-	16	12.5			
Intensive treatment (5 or more consecutive EDs‡) at first exposure	26	15.1	-	17	13.3			
FranceCoag Network[3]*	97			111				
High-risk *F8* gene defect regardless of the date of genetic diagnosis	62	63.9	+++	85	76.6			
High-risk *F8* gene defect known at first FVIII infusion§	23	23.7	+	30	27.0			
Family history of hemophilia and inhibitor regardless of date of appearance	9	9.3	+	15	13.5			
Family history of hemophilia and inhibitor known at first FVIII infusion§	6	6.2	-	6	5.4			
Ethnic origin: Others (not white only) not African or African American	17	17.5	+	23	20.7			
Ethnic origin: African or Afro-American (at least 1 grandparent)	6	6.2	-	3	2.7			
Peak treatment episode at first exposure ≥3 consecutive EDs‡	31	32.0	-	35	31.5			
Peak treatment episode at first exposure ≥5 consecutive EDs	14	14.4	+	21	18.9			
First exposure linked to surgical procedure (with ≥3 EDs)	2	2.1	-	1	0.9			
First exposure linked to severe bleeding episode	10	10.3	-	10	9.0			
At least 2 of the above-mentioned factors known at first FVIII infusion‖	27	27.8	-	30	27.0			
At least 3 of the above-mentioned factors known at first FVIII infusion‖	6	6.2	+	10	9.0			
FranceCoag Network: 3 selected HTCs (Lille, Necker, and Strasbourg)§	18			47				
High-risk *F8* gene defect known at first FVIII infusion	4	22.2	+	11	23.4			
Family history of hemophilia and inhibitor known at first FVIII infusion	3	16.7	—	3	6.4			
Ethnic origin: Others (not white only) not African or African American	6	33.3	-	14	29.8			
Ethnic origin: African or Afro-American (at least one grandparent)	3	16.7	—	0	0.0			
Peak treatment episode at first exposure ≥3 consecutive EDs‡	8	44.4	—	13	27.7			
Peak treatment episode at first exposure ≥5 consecutive EDs	2	11.1	++	10	21.3			
First exposure linked to surgical procedure (with ≥3 EDs)	0	0.0	+	1	2.1			
First exposure linked to severe bleeding episode	1	5.6	-	2	4.3			
At least 2 of the above-mentioned factors‖	8	44.4	—	10	21.3			
At least 3 of the above-mentioned factors‖	2	11.1	+	6	12.8			
FranceCoag Network: 30 remaining HTCs§	79			64				
High-risk *F8* gene defect known at first FVIII infusion	19	24.1	++	19	29.7			
Family history of hemophilia and inhibitor known at first FVIII infusion	3	3.8	+	3	4.7			
Ethnic origin: Others (not white only) not African or African American	11	13.9	+	9	14.1			
Ethnic origin: African or Afro-American (at least 1 grandparent)	3	3.8	+	3	4.7			
Peak treatment episode at first exposure ≥3 consecutive EDs‡	23	29.1	+	22	34.4			
Peak treatment episode at first exposure ≥5 consecutive EDs	12	15.2	+	11	17.2			
First exposure linked to surgical procedure (with ≥3 EDs)	2	2.5	-	0	0.0			
First exposure linked to severe bleeding episode	9	11.4	+	8	12.5			
At least 2 of the above-mentioned factors‖	19	24.1	++	20	31.3			
At least 3 of the above-mentioned factors‖	4	5.1	+	4	6.3			

*The risk factor designations used in the original articles have been kept.

†Δ is the difference between risk factor prevalences of adjacent columns: in support of confounding by indication (CbI) [+ (Δ>0), ++ (Δ>5), +++ (Δ>10)] or not in support of CbI [- (Δ<0), – (Δ<–5), — (Δ<−10)].

‡An exposure day (ED) was defined as a day during which one or more infusions of FVIII were given.

§Results not shown in the original article.

‖The factor "Peak treatment episode at first exposure ≥5 consecutive EDs" was not considered in this definition because it is redundant with the factor "Peak treatment episode at first exposure ≥3 consecutive EDs."

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To the editor:

Risk of inhibitors in previously untreated patients with hemophilia: a meta-analysis of literature studies

We read with interest the articles published by Calvez et al and Collins et al[1,2] reporting an increased inhibitor rate in previously untreated patients (PUPs) with severe hemophilia A receiving Kogenate FS compared with those receiving Advate.

These results somehow extended findings reported in the Research of Determinants of Inhibitor Development (RODIN) study,[3] and more recently, another study has been published on this topic.[4] Given similarities in the study design and population enrolled in the 4 studies, their results can be pooled together to provide an aggregate estimation of the inhibitor rate in this population.

Incidence rate (IR) and pooled odds ratio (OR) with 95% confidence intervals (CI) were calculated using a random-effect model, and heterogeneity was evaluated using I^2 statistics.

Separate analyses have been performed for inhibitors and high-titer (HT) inhibitors. To avoid duplicating data, patients enrolled in the RODIN[3] study were excluded from the other studies.[1,2]

To compare the crude IR between Kogenate FS and Advate, we calculated pooled OR instead of RR to allow an easier comparison with results of the adjusted analysis. A total of 865 PUPs (437 Kogenate FS, 428 Advate) were evaluated, with a follow-up period between 20 and 75 exposure days. Two hundred ninety patients developed inhibitors, with 169 HT inhibitors.

The IR of inhibitors was 0.393 (95% CI: 0.31, 0.48; I^2: 63.5%; $P = .042$) and 0.288 (95% CI: 0.24, 0.34; I^2: 37.9%; $P = .185$) for Kogenate FS and Advate, respectively. For HT inhibitors, the IR was 0.224 (95% CI: 0.19, 0.26; I^2: 0%; $P = .484$) and 0.176 (95% CI: