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LETTERS TO THE EDITORS

FVIII inhibitor development according to concentrate: data from the EUHASS registry excluding overlap with other studies

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Recently, analyses on inhibitor development according to concentrate in previously untreated patients (PUPs) from two national cohort studies have been published [1,2]. A similar analysis has been performed on the first 4 years of data collection of the European Haemophilia Safety Surveillance System (EUHASS) project [3]. Together with the initial report from the RODIN study published in 2013 [4], these publications provide data on a very considerable number of patients, almost exclusively originating from Europe.

Reporting to multiple registries is common, and a rare disease such as haemophilia is no exception. Although the FranceCoag study [1], the UKHCDO study [2] and the EUHASS study [3] excluded patients overlapping with the RODIN study from their analyses, the additional overlap between the EUHASS, the FranceCoag and UKHCDO studies has not been previously reported.

The analysis of non-overlapping data from the EUHASS study has the potential to contribute to the ongoing discussion about the perceived increased inhibitor risk associated with the use of specific recombinant Factor VIII concentrates. Thus, we hereby provide additional analyses of the data from the EUHASS study.

Data on inhibitor development in PUPs were collected from 1 October 2008 to 1 January 2013 from 57 European centres participating in the EUHASS study [3]. The design of the EUHASS study was described previously [5,6]. In short, data on inhibitor development in PUPs with severe haemophilia A (FVIII < 0.01 IU dL^{-1}) were reported every 3 months and data on the number of PUPs reaching 50 exposure days without developing an inhibitor were collected annually for each concentrate used. Inhibitors were defined by two positive tests according to the local laboratory. Patients with a titre equal or higher than 5 BU in the two-first two positive tests were defined as high titre inhibitors.

Month and year of birth were collected for inhibitor patients only.

Inhibitor incidence according to concentrate used was calculated for each concentrate used. To exclude overlap with the RODIN study, data on 120 patients reported until 1 October 2011 from centres participating in RODIN were excluded (Table 1). Subsequently, data on 55 PUPs from French centres and 44 PUPs from UK centres were excluded to provide the data on the 198 PUPs reported to EUHASS only. Details on inhibitor development according to concentrate type and brand for patients reported in the different studies and to EUHASS only are shown in Table 1.

Since the classification of high titre inhibitors in EUHASS is based only on the results of the first two tests, the proportion of high titre inhibitors in EUHASS is slightly underestimated. Overall 68/108 (63%) inhibitors reported were high titre inhibitors [cumulative incidence 16.3%; 95% confidence interval (95% CI) 12.9–20.2]. After exclusion of data reported in other studies, the overall cumulative incidence of high titre inhibitors was 14.6% (95% CI 10.0–20.4).

In the 198 patients reported to EUHASS only, the risk of inhibitor development of patients on Kogenate Bayer or Helixate NexGen was similar to that of patient treated with Advate.

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[1]EUHASS collaborators are listed in the Appendix

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[Correction added on 1 October 2015, after first online publication: R Hollingsworth has been added as the third author]

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Table 1. Inhibitor development according to concentrate for PUPs with severe haemophilia A.

	All EUHASS [3]		Overlap with RODIN [3,4]		Overlap with FranceCoag [1]		Overlap with UKHCDO [2]		Reported to EUHASS only			
									All inhibitors		High titre inhibitors	
	Inhibitor/at risk	P (95% CI)	Inhibitor/at risk	P (95% CI)	Inhibitor/at risk	P (95% CI)	Inhibitor/at risk	P (95% CI)	Inhibitor/at risk	P (95% CI)	Inhibitor/at risk	P (95% CI)
Total	108/417	25.9 (21.8–30.4)	38/120	31.7 (23.5–40.8)	17/55	30.9 (29.1–44.8)	11/44	25.0 (13.2–40.3)	42/198	21.2 (15.7–27.6)	29/198	14.6 (10.0–20.4)
FVIII recombinant overall	97/366	26.5 (22.1–31.3)	35/107	32.7 (24.0–42.5)	14/37	37.8 (22.5–55.2)	11/44	25.0 (13.2–40.3)	37/178	20.8 (15.1–27.5)	26/178	14.6 (9.8–20.7)
FVIII plasma derived	11/51	21.6 (11.3–35.3)	3/13	23.1 (5.0–53.8)	3/18	16.7 (3.6–41.4)	0/0	NA	5/20	25.0 (8.7–49.1)	3/20	15.0 (3.2–37.9)
Advate	37/141	26.2 (19.2–34.3)	15/56	26.8 (15.8–40.3)	5/13	38.5 (13.9–68.4)	4/13	30.8 (9.1–61.4)	13/59	22.0 (12.3–34.7)	7/59	11.9 (4.9–22.9)
Kogenate Bayer & Helixate NexGen	44/142	30.8 (23.3–39.0)	17/38	44.7 (28.6–61.7)	7/21	33.3 (14.6–57.0)	2/9	22.2 (2.8–60.0)	18/75	24.0 (14.9–35.3)	14/75	18.7 (9.8–20.7)
Recombinate	1/24	4.2 (0.1–21.1)	0/0	NA	0/0	NA	0/0	NA	1/24	4.2 (0.1–21.1)	1/24	4.2 (0.1–21.1)
Refacto	0/6	0.0 (0.0–45.9)	0/5	0.0 (0.0–52.2)	0/0	NA	0/0	NA	0/1	0.0 (0.0–97.5)	0/1	0.0 (0.0–97.5)
Refacto AF	15/52	28.8 (17.1–43.1)	3/8	37.5 (8.5–75.5)	2/3	66.7 (9.4–99.2)	5/22	22.7 (7.8–60.0)	5/19	26.3 (9.1–51.2)	4/19	21.1 (6.1–45.6)
	RR	95% CI							RR	95% CI	RR	95% CI
Kogenate & Helixate vs. Advate	1.18	(0.81–1.71)							1.09	0.58–2.04	1.57	0.68–3.60

Values are numbers, or proportions (P) or relative risks (RR) with 95% confidence intervals (95% CI).
PUPs, previously untreated patients; EUHASS, European Haemophilia Safety Surveillance System; FVIII, factor VIII.

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Disclosures

K Fischer has acted as a consultant and participated in expert groups for Bayer, Baxter, Biogen Idec, CSL Behring, NovoNordisk and Pfizer, has received research grants from Baxter, NovoNordisk, Pfizer, and has given invited educational lectures for Bayer, Baxter, NovoNordisk, Octapharma and Pfizer, and has received travel support from Baxter and Bayer. A Iorio has received research grants from Bayer, Baxter and Pfizer and honoraria for advisory board participation and invited educational lectures from Bayer, Baxter and Pfizer. M Makris has acted as consultant to CSL Behring and NovoNordisk. He took part in an Advisory Panel organised by BPL and gave lectures for Baxter, Bayer, Biogen Idec, Biotest, Octapharma, Pfizer and SOBI. He has received travel support from Baxter and Bayer.

References

1 Calvez T, Chambost H, Claeyssens-Donadel S *et al.* Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A. *Blood* 2014; **124**: 3398–408.

2 Collins PW, Palmer BP, Chalmers EA *et al.* Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe hemophilia A, 2000-2011. *Blood* 2014; **124**: 3389–97.

3 Fischer K, Lassila R, Peyvandi F *et al.* Inhibitor development in haemophilia according to concentrate. Four-year results from the European HAemophilia Safety Surveillance (EUHASS) project. *Thromb Haemost* 2015; **113**: 968–975.

4 Gouw SC, Van der Bom JG, Ljung R *et al.* Factor VIII products and inhibitor development in severe hemophilia A. *N Engl J Med* 2013; **368**: 231–9.

5 Makris M, Calizzani G, Fischer K *et al.* EUHASS: the European Haemophilia Safety Surveillance system. *Thromb Res* 2011; **127** (Suppl. 2): S22–5.

6 Fischer K, Lewandowski D, Van den Berg HM, Janssen MP. Validity of assessing inhibitor development in haemophilia PUPs using registry data: the EUHASS project. *Haemophilia* 2012; **18**: e241–6.

Appendix: Collaborators for EUHASS study

EUHASS centres, alphabetical order, 2 people per centre: Director followed by main data submitter (if there was one apart from the Director)

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