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ORIGINAL ARTICLE

Inhibitor development according to concentrate after 50 exposure days in severe hemophilia: data from the European HAemophilia Safety Surveillance (EUHASS)

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Abstract

Background: Patients with hemophilia have a life-long risk of developing neutralizing antibodies (inhibitors) against clotting factor concentrates. After the first 50 exposure days (EDs), ie, in previously treated patients (PTPs), data on inhibitor development are limited.

Objectives: To report inhibitor development according to factor (F)VIII or FIX concentrate use in PTPs with severe hemophilia A and B.

Methods: Inhibitor development in PTPs was collected since 2008 from 97 centers participating in European HAemophilia Safety Surveillance. Per concentrate, inhibitors were reported quarterly and the number of PTPs treated annually. Incidence rates (IRs)/1000 treatment years with 95% CIs were compared between concentrate types (plasma derived FVIII/FIX, standard half-life recombinant FVIII/FIX, and extended half-life recombinant (EHL-rFVIII/IX) concentrates using IR ratios with CI. Medians and IQRs were calculated for inhibitor characteristics.

Results: For severe haemophilia A, inhibitor rate was 66/65,200 treatment years, IR 1.00/1000 years (CI 0.80-1.30), occurring at median 13.5 years (2.7-31.5) and 150 EDs (80-773). IR on plasma-derived pdFVIII (IR, 1.13) and standard half-life recombinant FVIII (IR, 1.12) were similar, whereas IR on EHL-rFVIII was lower at 0.13 (incidence rate ratio, 0.12; 95% CI, <0.01-0.70; $P < .01$).For severe hemophilia B, inhibitor rate was 5/11,160 treatment years and IR was 0.45/1000 years (95% CI, 0.15-1.04), at median 3.7 years (95% CI, 2.1-42.4) and 260 EDs (95% CI, 130 to >1000). Data were insufficient to compare by type of FIX concentrates.

Conclusion: Low inhibitor rates were observed for PTPs with severe hemophilia A and B. Data suggested reduced inhibitor development on EHL-rFVIII, but no significant difference between plasma-derived FVIII and standard half-life recombinant FVIII. FIX inhibitor rates were too low for robust statistical analysis.

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antibodies, factor VIII, hemophilia A, hemophilia B, inhibitor, neutralizing factor, PTP, registries

Essentials

- Neutralizing antibodies (inhibitors) to factor (F)VIII/IX may still develop after 50 exposure days.
- Inhibitor risk in severe hemophilia was assessed in 65,200 FVIII and 11,160 FIX treatment years.
- Inhibitor risk was low at 1.00/1000 years for hemophilia A and 0.45/1000 years for hemophilia B.
- Data showed an 88% (confidence interval 30%-99%) lower inhibitor risk on extended half-life FVIII.

1 | INTRODUCTION

Congenital hemophilia A and B are due to reduced activity of factor (F)VIII and FIX, respectively. Until recently their treatment was largely through the infusion of FVIII or FIX concentrates. Concentrates can be plasma derived when purified from human plasma or produced by recombinant technology. Recombinant products can have standard half-life which is very similar to that of plasma derived concentrates or they can be modified *in vitro* to extend their half-life.

The development of neutralizing anti-FVIII/IX antibodies, termed inhibitors, is the most serious complication of concentrates nowadays.

Subjects with hemophilia treated for less than 50 days are termed previously untreated patients (PUPs), whilst those treated for longer are known as previously treated patients (PTPs).

Development of inhibitory antibodies against clotting factor concentrates has largely been reported during the first 50 exposure days (EDs). Up to 50 EDs, inhibitors develop in around 25% to 30% [1] and 8% to 10% [2] of patients with severe hemophilia A and B, respectively. After this period, inhibitors develop much less frequently but still interfere with the efficacy and half-life of prophylactic and on-demand treatment with concentrate.

Within the first 50 EDs, studies comparing inhibitor development according to different FVIII and FIX concentrates are challenging due to low patient numbers [3–6]. This is even more difficult after the first 50 EDs in PTPs when inhibitor development is much less frequent [1,2,4,7].

The European HAemophilia Safety Surveillance (EUHASS) project was established in 2008 and designed to assess side effects of treatment in all patients with inherited bleeding disorders. The present analysis aimed to update the previous report on inhibitor development according to FVIII/FIX concentrates after 50 EDs in patients with severe hemophilia [4].

2 | METHODS

Data on the inhibitor development in PTPs with severe hemophilia were collected from October 1, 2008, to January 1, 2023, in 14 years from 97 European centers participating in the EUHASS registry. The list of participating centers is provided in the supplementary material. The design of the EUHASS was described previously [8,9]. In short, anonymized data on inhibitor development in individual patients with severe hemophilia A or B (FVIII/IX < 0.01 IU/dL) were reported every 3 months, and data on the number of PTPs treated according to diagnosis and concentrate were reported at group level at annual intervals. Consequently, information on age and EDs was only available for those with a positive inhibitor. Inhibitors were defined by 2 positive tests according to the local laboratory. Month and year of birth were collected for inhibitor patients only. EDs were recorded up to 1000 EDs and coded as more than 999 EDs for patients with 1000 EDs or more. Prior to study entry, all centers approached their institutional review board for approval, which was obtained, if required. Logical checks and verification for data for all adverse events were performed at submission, and logical checks and verification for data on number of patients at risk were done before analysis.

2.1 | Statistical analyses

Inhibitor rates/1000 treatment years with 95% CIs were calculated for concentrate type (plasma-derived [pd], recombinant-standard half-life [r-SHL], recombinant extended half-life [r-EHL], individual concentrate using the Exact method). Kogenate FS and Helixate NextGen were considered as having the same concentrates. Comparisons between categories or concentrates (incidence rate ratios [IRRs] with their CI) were made using Medcalc [10]. Medians and IQRs (P25-P75: IQR) were calculated for inhibitor characteristics. Descriptive statistics were performed using SPSS Version 29.0.

3 | RESULTS

3.1 | Inhibitor development in PTPs with severe hemophilia A

For PTPs with severe hemophilia A, EUHASS collected 68,708 treatment years, of which 65,200 were on clotting factor concentrates, including 9 SHL-rFVIII, 4 EHL-rFVIII, and 20 pdFVIII concentrates (Table 1). Overall, inhibitors occurred in 66 patients, resulting in an incidence rate (IR) of 1.00/1000 treatment years with FVIII concentrates (95% CI, 0.80-1.30). Inhibitors occurred at a median age of 13.5 years (IQR, 2.7-37.5; range, 0.4-81.9 years) after a median of 150 EDs (IQR, 80-773; range, 51 to >1000). Inhibitor development in hemophilia A and B according to age is shown in the Figure It was apparent that, although all patients had >50 EDs, 26% of FVIII inhibitors and 40% of FIX inhibitors developed before the age of 3 years, and inhibitor development remained stable onwards. No peak was observed after age 59 years.

When comparing the categories of FVIII concentrates, the inhibitor rates of pd FVIII and SHL-rFVIII were similar at 1.13 and 1.12/1000 treatment years, respectively (IRR, 1.01; 95% CI, 0.56-1.75; $P = .96$). Inhibitor development on EHL-rFVIII was significantly lower than in SHL-rFVIII (0.13 vs 1.12/1000 treatment years) with an IRR of 0.12 (95% CI, <0.01-0.70; $P < .01$). The comparison between individual concentrates was hindered by the large number of concentrates used. Only individual concentrates with more than 5000 treatment years were compared using Advate as the reference. Inhibitor development on Kogenate or Helixate NexGen was similar to Advate at 0.94 vs 1.11/1000 treatment years (IRR, 0.85; 95% CI, 0.35-1.96, $P = .70$). Inhibitor development on Refacto AF at 1.52/1000 treatment years appeared increased, but with a wide overlap in the CIs (IRR, 1.37; 95% CI, 0.63-2.96; $P = .38$). Inhibitor development on Elocta (0.18/1000 treatment years) was 83% lower than on Advate with an IRR of 0.17 (95% CI, <0.01-1.06; $P = .04$). Of note, this inhibitor on Elocta developed after 74 EDs at the age of 8 months.

3.2 | Inhibitor development in PTPs with severe hemophilia B

For PTPs with severe hemophilia B, EUHASS collected 11,160 treatment years, including 2 SHL-rFIX, 3 EHL-rFIX, and 13 pdFIX concentrates (Table 2). Inhibitors were reported only in 5 patients, resulting in an IR of 0.45/1000 treatment years (95% CI, 0.15-1.05). Inhibitor development according to age and diagnosis is shown in the Figure. Inhibitors occurred early, at a median age of 3.7 years (IQR, 2.1-42.4; range, 1.9-52.6 years) after a median of 260 EDs (IQR, 130 to >1000; range, 60 to >1000). At the time of inhibitor development, no allergic reactions were reported in these 5 patients. From Table 2, it can be appreciated that number of treatment years for categories of FIX concentrates as well as for individual FIX concentrates were too low to make reliable comparisons and that most CIs showed a wide overlap.

4 | DISCUSSION

4.1 | Main findings

During 14 years of data collection in 97 European hemophilia treatment centers, 65,200 treatment years on 42 FVIII concentrates and 11,160 treatment years on 18 FIX concentrates have been collected. Low inhibitor rates were observed in PTPs both with severe hemophilia A (IR: 1.00/1000 treatment years) and hemophilia B (IR: 0.45/1000 treatment years).

For hemophilia A, our main observation was the reduced inhibitor rates for patients treated with EHL-rFVIII (IR, 0.13/1000 treatment years) compared with SHL-rFVIII (IR, 1.12/1000 treatment years) with an IRR of 0.12 (95% CI, <0.01-0.70; $P < .01$). Inhibitor development was similar for pdFVIII and SHL-rFVIII (IRR, 1.01; 95% CI, 0.56-1.75; $P = .96$). Inhibitor development did not increase with age in patients aged >59 years. For hemophilia B, the patient numbers were still too limited to enable comparison of even the categories of, or individual FIX concentrates.

4.2 | Internal and external validity/strengths and weaknesses

The present data have high external validity as it represents the largest body of data collected on inhibitor development in PTPs including data from 97 European treatment centers, all with a wide selection of clotting factor concentrates and varying treatment strategies available. At the same time, since inhibitor development in PTPs is a rare event, the present data illustrate the difficulty in comparison of inhibitor development on individual concentrates, even in a very large registry such as EUHASS. As 25% of inhibitor patients were reported to have 51 to 80 EDs at the time of inhibitor diagnosis, all our patients may not be uniformly defined as true PTPs, and the IR may be overestimated in the present study. Unfortunately, we cannot solve this issue, as EUHASS only collects denominator data (for those without inhibitors) in 2 categories: before 50 EDs and after 50 EDs.

On the other hand, this potential misclassification may not have a significant effect on our conclusions, as it has been established that inhibitor development is most frequent in the first 50 EDs, ie, in PUPs.

TABLE 1 Inhibitor development according to factor (F)VIII concentrates.

Concentrate	Inhibitor	Treatment years	P/1000 treatment years	Lower CI	Upper CI
All hemophilia A treated with FVIII	66	65,200	1.00	0.80	1.30
Standard half-life recombinant FVIII	46	40,966	1.12	0.82	1.50
Extended half-life recombinant FVIII	1	7436	0.13	0.00	0.75
Plasma-derived FVIII	19	16,798	1.13	0.68	1.77
Advate	17	15,410	1.11	0.64	1.77
Afstyla	0	547	0.00	0.00	6.72
Kogenate/Helixate	10	10,626	0.94	0.45	1.73
Kovaltry	0	1803	0.00	0.00	2.04
NovoEight	0	2205	0.00	0.00	1.67
Nuwiq	1	544	1.84	0.05	10.20
Recombinate	0	396	0.00	0.00	9.27
Refacto	4	208	19.23	5.26	48.50
Refacto antihemophilic factor	14	9227	1.52	0.83	2.54
Adynovi/Adynovate	0	945	0.00	0.00	3.90
Elocta (Eloctate)	1	5467	0.18	0.00	1.02
Esperoct (N8-GP)	0	525	0.00	0.00	7.00
Jivi	0	499	0.00	0.00	7.37
Aafact	1	412	2.43	0.06	13.45
Alphanate	0	65	0.00	0.00	55.17
Amofil	0	60	0.00	0.00	59.63
Beriate	1	1820	0.55	0.01	3.06
Emoclot	2	1759	1.14	0.14	4.10
Factane (LFB)	0	922	0.00	0.00	3.99
Factor 8Y (BPL)	0	157	0.00	0.00	23.22
Haemate P	1	1509	0.66	0.02	3.69
Faktor VIII SDH Intersero	0	45	0.00	0.00	78.71
Fanhdi	4	2951	1.36	0.37	3.47
Haemoctin SDH	3	677	4.43	0.91	12.90
Hemophil M	1	90	11.11	0.28	60.36
Humaclot	0	70	0.00	0.00	51.33
Immunate	3	2511	1.19	0.25	3.49
Klott	0	277	0.00	0.00	13.23
Koate DVI	1	97	10.31	0.26	56.10
Octanate (LV)	2	2995	0.67	0.08	2.41
Replenate	0	1	0.00	0.00	975.00
Voncento	0	179	0.00	0.00	20.40
Wilate	0	401	0.00	0.00	9.16

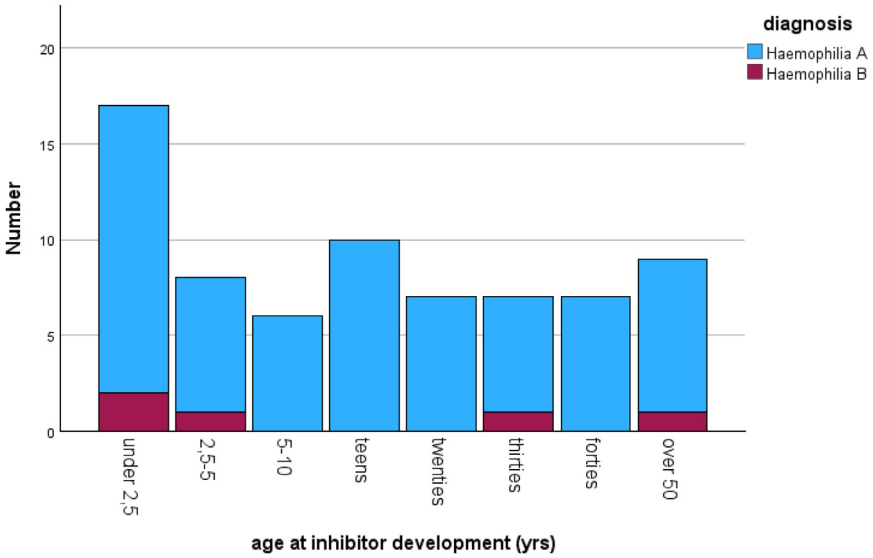

FIGURE Age at inhibitor development after 50 exposure days according to diagnosis.

The most detailed data on this issue have been reported from the prospective European (Pediatric Treatment Network) PedNet cohort: 96% of inhibitors in 1038 PUPs with severe hemophilia A [1] and 86% of inhibitors in 154 PUPs with severe hemophilia B had developed before 50 EDs [2].

4.3 | Comparison with previous literature

The PedNet report on severe hemophilia A included 4031 treatment years in 524 PTPs followed between 75 and 1000 EDs [1]. During this period, 2 inhibitors were reported, resulting in an IR of 0.50 (95% CI, 0.06-1.79), which is similar to the overall inhibitor rate in hemophilia A observed in the present study: IRR was 0.49 (95% CI, 0.06-1.84; P = .32).

The most recent meta-analysis reporting on inhibitor development in PTPs was performed by Hassan et al. [7] who included patients with hemophilia A having FVIII of <0.02 IU/dL and a minimum of 50 EDs [7]. They analyzed 41 studies reporting 39 inhibitors in 19,157 treatment years, resulting in a higher IR than in the present study: 2.01 (95% CI, 1.32-3.03). In this meta-analysis, data suggested differences in inhibitor development between several SHL-rFVIII concentrates, without sufficient power to identify statistically significant differences.

In the analysis of the first 4 years of EUHASS [4], we observed 26 inhibitors in 17,667 treatment years, resulting in a higher IR of 1.5/1000 years (95% CI, 1.0-2.2) and an IRR of 1.45 (95% CI, 0.89-2.32; P = .11) compared with the present data. The trend toward a lower reported inhibitor rate for hemophilia A in this longer capture time of 14 years of EUHASS may also be attributed to the change in treatment landscape: some older concentrates associated with increased inhibitor development were taken off the market and new concentrates, including EHL-rFVIII, may carry a lower inhibitor risk.

In 2011, Hay et al. [11] reported on overall inhibitor development rates in severe hemophilia A (SHA) collected over 20 years in United Kingdoms' national hemophilia registry. Unfortunately, PUPs and PTPs were not reported separately, but Hay et al. [11] reported a bimodal age distribution, with a first peak at the onset of treatment, and a second peak in patients older than 59 years. In this older age cohort, 17 inhibitors were reported in 1621 treatment years, resulting in a very high IR of 10.49 (95% CI, 6.12-16.74). As in EUHASS only 5 inhibitors in SHA were reported after age 59 years, the present study does not corroborate the finding of the second peak in inhibitor development, nor can it calculate age-specific inhibitor rates since age is collected only in the inhibitor patients. As is observed in the Figure, the present data show an even distribution of age at inhibitor development after around 3 years and above.

For hemophilia B, the analysis of the first 4 years of EUHASS showed very similar data to the present analysis: we observed 1 inhibitor in 2837 treatment years, resulting in an IR of 0.35/1000 treatment years (95% CI, 0.01-1.96) [4]. Compared with the present data, the IRR was 0.79 (95% CI, 0.02-7.03; P = .91). Unfortunately, we could not identify any other reports on IRs of FIX inhibitor development in PTPs, and further comparisons could not be made. Although the report on FIX inhibitors from PedNet included 2 inhibitors which developed between 50 and 500 EDs [2], and the number of treatment years was not provided.

4.4 | Clinical implications

Data on inhibitor development on FVIII/FIX concentrates remain relevant, even in the changing treatment landscape. Although non–factor replacement treatment options have recently been introduced and are under development for both hemophilia A and B, clotting factor concentrates will still be used by many patients, because non–

TABLE 2 Inhibitor development according to factor (F)IX concentrates.

Concentrate	Inhibitor	Treatment years	P/1000 treatment years	Lower CI	Upper CI
All hemophilia B treated with FIX	5	11,160	0.45	0.15	1.05
Standard half-life FIX	3	5267	0.57	0.12	1.66
Extended half-life FIX	1	2780	0.36	0.01	2.00
Plasma derived FIX	1	3113	0.30	0.01	1.79
Benefix	3	5179	0.58	0.12	1.69
Rixubis	0	88	0.00	0.00	41.05
Alprolix	0	1619	0.00	0.00	2.28
Idelvion	1	888	1.13	0.03	6.26
Refixia	0	273	0.00	0.00	13.42
Alphanine	0	60	0.00	0.00	59.63
Berinin	0	101	0.00	0.00	35.86
BETAFACT	0	494	0.00	0.00	7.44
FIX Grifols	0	41	0.00	0.00	86.04
Faktor IX SDN (Biotest)	0	2	0.00	0.00	841.89
Haemonine	1	31	32.26	0.82	167.02
Immunine	0	1011	0.00	0.00	3.64
Mononine	0	128	0.00	0.00	28.41
Nanofix	0	53	0.00	0.00	67.23
Nanotiv	0	32	0.00	0.00	108.88
Nonafact	0	57	0.00	0.00	62.67
Octanine	0	1064	0.00	0.00	3.46
Replenine VF	0	39	0.00	0.00	16.39

F, factor; SDN, __; VF,___.

replacement therapies need to be combined with clotting factor concentrates in case of major surgery or bleeding events, while gene therapies have only recently been introduced and may not provide sufficient clotting factor expression in all individuals due to variability of efficacy.

The data suggesting reduced inhibitor development for especially rFVIII-Fc were statistically significant but are based on still a relatively small data set. Previous preclinical and clinical studies on the impact of Fc fusion on the immunogenicity of clotting factors FVIII and FIX have generated inconsistent results [12–17]. A recent analysis of inhibitor development in PUPs with SHA from EUHASS included only 54 PUPs on rFVIII-Fc and did not show reduced inhibitor development compared with Advate [17]. For PTPs treated with rFIX-Fc, no inhibitors were observed during 1619 treatment years (IR, 0/1000 treatment years; 95% CI, 0-2.28), but this IR still overlapped with the most widely used rFIX Benefix (IR, 0.58/1000 treatment years; 95% CI, 0.12-1.69), so no conclusions can be drawn. Moreover, a detailed analysis including patient specific risk factors such as personal and/or family history of inhibitors and mutation is needed before treatment choices for individual patients can be made. Such data can only be generated by, preferably national, registries including detailed information on risk factors for inhibitor development.

5 | CONCLUSION

In conclusion, the EUHASS registry data collected over 14 years show low inhibitor rates in PTPs with severe hemophilia A (IR, 1.00/1000 treatment years) and hemophilia B (IR, 0.45/1000 treatment years).

For hemophilia A, data showed similar inhibitor rates between those patients treated with pdFVIII and SHL-rFVIII. However, the inhibitor rates for the patients treated with EHL-rFVIII were significantly reduced compared with SHL-rFVIII with an IRR of 0.12 (95% CI, <0.01-0.70; $P < .01$). For hemophilia B, numbers were still too limited to compare categories of or individual FIX concentrates.

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AUTHOR CONTRIBUTIONS

All authors conceived and designed the study. M.M., R.H., D.C., and K.F. coordinated and performed data checking. K.F. planned and undertook the statistical analyses. All authors performed data interpretation. K.F. drafted the manuscript, which was completed with input from all authors. All the authors approved the final manuscript.

Data collection was performed by K.F., R.L., F.P., A.G., T.L., S.G., M.M., and all centers collaborating in the EUHASS registry. As manager of EUHASS, D.C. is responsible for database maintenance as well as dealing with queries and analyses. Lists of collaborators to the EUHASS registry are provided in the Supplementary Material.

RELATIONSHIP DISCLOSURE

K.F. has acted as a consultant and participated in expert groups for Bayer, Biogen, CSL Behring, Novo Nordisk, and SOBI, has received research grants from Bayer, Novo Nordisk, Pfizer, and has given invited educational lectures for Bayer, Novo Nordisk, and Pfizer, and has received travel support from Sobi and Bayer. R.L. received honoraria for advisory board participation for Novo Nordisk, Pfizer, and Sanquin. F.P. has received honoraria for invited educational lectures from Novo Nordisk, CSL Behring, Bayer, and Baxter, in addition, she has received research support from Novo Nordisk. A.G. reported no competing interests.

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