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Inhibitor development in non-severe haemophilia across Europe

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Abstract

Background: Evidence about inhibitor formation in non-severe haemophilia and the potential role for clotting factor concentrate type is scant.

Aim: To report inhibitor development in non-severe haemophilia patients enrolled in the European Haemophilia Safety Surveillance (EUHASS) study.

Methods: Inhibitors are reported quarterly and total treated patients annually. Incidence rates and 95% Confidence Intervals (95% CI) were calculated according to diagnosis and concentrate used.

Results: Between 1-10-2008 and 31-12-2012, 68 centres reported on 7969 patients with non-severe haemophilia A and 1863 patients with non-severe haemophilia B. For haemophilia A, 37 inhibitors occurred in 8622 treatment years, resulting in an inhibitor rate of 0.43/100 treatment years (95% CI 0.30-0.59). Inhibitors occurred at a median age of 35 years, after a median of 38 exposure days (EDs; P25-P75: 20-80); with 72% occurring within the first 50 EDs. In haemophilia B, one inhibitor was detected in 2149 treatment years, resulting in an inhibitor rate of 0.05/100 years (CI 0.001-0.26). This inhibitor developed at age 6 years, after 6 EDs. The rate of inhibitors appeared similar across recombinant and plasma derived FVIII concentrates. Rates for individual concentrates could not be calculated at this stage due to low number of events.

Conclusion: Inhibitors in non-severe haemophilia occur three times more frequently than in previously treated patients with severe haemophilia at a rate of 0.43/100 patient years (haemophilia A) and 0.05/100 years (haemophilia B). Although the majority of Inhibitors developed in the first 50 EDs, inhibitor development continued with increasing exposure to FVIII.

Introduction:

Haemophilia is a rare disease affecting 1 in 10,000 (haemophilia A) and 1 in 50,000 (haemophilia B) individuals, of which 50-60% have moderate or mild disease with Factor VIII or IX activity levels of 1-40%(1-3) . Since the development of cryoprecipitate in the 1960s and clotting factor concentrates in the 1970s, effective replacement therapy is available. This together with the development of home-treatment and prophylaxis has dramatically improved outcome and quality of life(4-5). Since the introduction of viral inactivation in the mid-1980s, the development of anti-factor VIII inhibitors has remained as the most frequent adverse effect of haemophilia treatment, especially in severe haemophilia A. During the first 50 exposure days (ED) to concentrate 25-32% of patients with severe haemophilia A and 5-10% of patients with severe haemophilia B develop inhibitors(6-8) . In patients with longer exposure to factor concentrates (previously treated patients) a lower incidence of 1-5 per 1000 treatment years was observed(9).

Based on much less data than in severe haemophilia, the cumulative incidence of inhibitor development in moderate and mild haemophilia is estimated to be 3-13% (10-12) . Several national registries reported that 28-29% of all inhibitors reported occurred in non-severe haemophilia patients(13-14). In clinical practice, inhibitors often cause spontaneous and major bleeding complications, as endogenous FVIII activity is reduced in the majority of patients, often to the level of severe haemophilia(14). Data on results of eradication treatment are lacking(10).

Non-severe haemophilia patients may have a lower inhibitor risk due to the combination of less frequent exposure to treatment and the presence of endogenous FVIII/FIX activity since before birth, which may induce tolerance. In addition to endogenous risk factors such as FVIII gene mutation, which has been shown to correlate to inhibitor risk both in severe(15) and in non-severe patients(12), treatment-related factors such as intensive treatment are also important determinants of inhibitor risk(16-17). In this context, many have proposed a role for FVIII concentrate type in inhibitor development. However, these reports have almost exclusively focused on severe patients. In this patient group, contradictory data have been published suggesting increased inhibitor development on recombinant FVIII concentrates compared to plasma derived FVIII concentrates(18-19); and on Kogenate Bayer/Helixate NextGen in previously untreated patients (PUPs) (20-23) , as well as on the role of B-domain deleted products (BDD rec FVIII)/Refacto and inhibitor risk in previously treated patients (PTPs)(9,24-25) .

Treatment related adverse events, including inhibitor development, are best addressed by prospective surveillance strategies or large cohort studies(8,26) The European Haemophilia Safety Surveillance (EUHASS) commenced in 2008 to monitor treatment safety in a large number of sentinel haemophilia centres in Europe(23,27).

The present study presents the first four-year results of monitoring for inhibitor development in non-severe haemophilia in the EUHASS registry.

Methods:

The design of the EUHASS study has already been reported (27). EUHASS is an international multicentre pharmaco-surveillance system covering an open population. Briefly, data collection started on October 1st 2008, or subsequent years for centres that joined EUHASS later. Participating centres provided reports on all new inhibitors diagnosed at the centre every three months, using a secure web-based data-entry system. Inhibitors were defined as two consecutive tests above the local laboratory threshold; information on recovery tests was not collected, nor was central laboratory confirmation performed. For each patient with an inhibitor, anonymised data on age, type and severity of haemophilia, cumulative number of EDs to FVIII/FIX concentrate before inhibitor development (for each concentrate used), the date of the last negative inhibitor titre, the dates and titres of the first two positive inhibitor titres, the type of inhibitor test used, and the local threshold for positive inhibitor testing were collected. EDs were recorded up to 1000 EDs, and coded as >999 EDs for patients with 1000 EDs or more. Only new inhibitors with positive titres on two occasions were considered.

Data on the number of patients at risk of inhibitor development are collected annually.

For patients with mild and moderate haemophilia, the number of patients receiving treatment without inhibitor development is established by subtracting the number of severe haemophilia patients treated from the total number of patients treated in the year; this calculation is performed for the whole population and for each concentrate. As details on the number of exposures at patient level are unavailable, exposure to concentrates is expressed as treatment years.

Logical checks, as well as checks for completeness of data are performed on each adverse event at the time of reporting. In 2013, all centres were asked to confirm accuracy and completeness of their data on adverse events and patients at risk entered up to 31st December 2012. Only data from centres with fully checked data and resolution of all queries are included in this analysis. Prior to study entry all centres had to approach their institutional review board for approval. Regulations in the 26 European Countries participating vary and for the majority of centres no formal approval was required. If required, approval was obtained before study participation.

Statistical analysis:

As some of the variables had a skewed distribution, descriptive statistics were presented as medians and interquartile ranges (presented as P25-P75). The inhibitor rate per 100 treatment-years was

calculated for each concentrate. The total observation period was 4.25 years, as the fourth year of the registry covered the period from 1st Oct 2011 to 31st December 2012. 95% Confidence Intervals (CI) were calculated using the exact method (28). All analyses were performed using SPSS version 20.

Results

The number of centres reporting full data on non-severe haemophilia patients increased since 2008 from 49 to 74. Failure to confirm submitted data resulted in exclusion of all data from six centres, which reported an additional eight inhibitors without providing denominator data. The dataset used for this report represents 92% of centres, 90% of registered patients and 83% of all inhibitors reported in non-severe haemophilia patients. An overview of data analysed and inhibitors reported according to diagnosis is shown in Table 1.

In total, these centres reported on 7969 patients with moderate or mild haemophilia A (8622 treatment years, 39 inhibitors) and 1863 patients with moderate or mild haemophilia B (2149 treatment years, 1 inhibitor).

Characteristics of patients developing inhibitors and the number of inhibitors are shown in Table 2. In patients with non-severe haemophilia A, 14 (36%) of inhibitors were observed in patients with moderate haemophilia (FVIII activity 1-5%) and 25 (64%) in patients with mild haemophilia (FVIII activity 6-40%). Patients developed inhibitors at a median age of 35.3 years, after a median of 38 EDs (P25-P75: 20-80); 72% (28/39) of inhibitors occurred before reaching 50 EDs, but 15% occurred after the first 100 EDs. The median first inhibitor titre was 4 BU/mL, including 51% with a high titre inhibitor (above 5 BU/mL). One inhibitor was observed in a patient with mild haemophilia B; this inhibitor developed at age 26 years, only after 6 EDs. Inhibitor rates between moderate and mild haemophilia patients could not be compared as treatment data were reported according to concentrate only, and not according to haemophilia severity.

Inhibitor development according to concentrate types and individual recombinant concentrates is shown in Table 3. The 39 inhibitors observed in patients with haemophilia A included 34 in patients treated with recombinant FVIII and five inhibitors in patients treated with plasma-derived concentrates. These included two inhibitors in patients with moderate haemophilia A treated with Haemate P. EUHASS collects data on number of haemophilia patients treated with Haemate P per year. However it was observed that the numbers of patients treated with Haemate P reported were inconsistent in many of the centres, possibly caused by inadverted inclusion of patients with von Willebrand disease in the annual reports. Therefore it was decided that the inhibitor rate for

Haemate P could not be reliably calculated from the current data, and data on Haemate P were excluded from the calculations of inhibitor rates in non-severe haemophilia A.

The 37 inhibitors analysed occurred in 8622 treatment years, resulting in an inhibitor rate of 0.43/100 treatment years (CI 0.30-0.59). As not all patients received clotting factor concentrates each year, the annual inhibitor rate for patients registered was lower at 0.11/100 patients/year. When comparing inhibitor development according to concentrate, the inhibitor rate appeared lower in patients treated with plasma-derived concentrates, but with overlapping 95% confidence intervals (0.52/100 years (CI 0.36-0.73) for recombinant concentrates and 0.14/100 years (CI 0.03-0.42) for plasma derived concentrates. After exclusion of data on Haemate P, inhibitors developed on only two (Aafact and Factane) of 15 plasma derived concentrates with a total number of treatment years ranging from 3 to 580 per concentrate and overlapping confidence intervals for inhibitor rates (Aafact 3.48/100 years (CI 0.09-17.92) and Factane (0.70/100 years (CI 0.08-2.51)). Details on inhibitor development on plasma derived FVIII and FIX concentrates are shown in the appendix. Plasma-derived concentrates were used in almost all centres.

For patients with non-severe haemophilia B, only one inhibitor was detected in 2149 treatment years, resulting in an inhibitor rate of 0.05/100 treatment years (CI 0.001-0.26). The annual inhibitor rate according to the number of patients registered was 0.011/100 patients/year. Due to the limited number of treatment years, comparisons between different concentrates are unreliable. In total, 12 different plasma-derived FIX concentrates were used, with a total number of treatment years ranging from 4 to 334 per concentrate (Table 4).

Discussion:

Main findings

With data on 10771 treatment years in 9832 patients with non-severe haemophilia under surveillance, the present study reports on inhibitor development in one of the largest prospectively collected cohorts to date.

For patients with non-severe haemophilia A the inhibitor rate was approximately 5 per 1000 treatment years, and for haemophilia B 10 times less. Although more than half of the Inhibitors in haemophilia A developed in the first 50 EDs, inhibitor development continued with increasing exposure to FVIII. Inhibitor development rates were similar across currently available FVIII concentrates.

Study design

The design used in the present study has strengths and weaknesses. An important strength is the prospective data collection from a large number of centres throughout Europe, including centres of different size and countries using different treatment strategies. This variability increases the generalizability of the results and is in sharp contrast with national studies, which have more homogeneous treatment strategies, and international studies, which predominantly include large centres(7,20,29).

Limitations include the lack of source data verification, the lack of detailed data on both inhibitors and non- inhibitors, and the unknown number of individual patients receiving treatment. As EUHASS was aimed to accrue large numbers of patients, we could not perform source data verification, collect data on additional risk factors for inhibitor development (such as treatment intensity, gene mutation or family history of inhibitors), or perform central confirmatory testing for inhibitors. Indeed, data control other than logical checks was not included in the original protocol. This was acknowledged and corrected during the project: all reports of adverse side effects are checked for logical mistakes, and all centres were asked to review their data and answer queries for the present analysis. Most centres checked their data and answered our queries, resulting in inclusion of 92% of centres and 83% of inhibitors reported. Only for Haemate P data still appeared inconsistent, and therefore it was decided not to calculate inhibitor rates for this concentrate. To address this issue, the electronic data collection system will be adapted.

Lack of information on the number of individual patients receiving treatment during the four years of observation does not affect the calculation of inhibitor risk per treatment year, but it prevents us from making any estimation of the cumulative incidence of inhibitors in non-severe haemophilia, which is more relevant from the individual patients' perspective. Likewise, lack of information on the number of EDs in the non-inhibitor patients makes it impossible to reliably estimate the cumulative

incidence of inhibitors during the first 50 EDs for non-severe patients. This makes it impossible to compare these data to the inhibitor rates in PUPs and PTPs with severe haemophilia. Only the data regarding the number of EDs at inhibitor development are unaffected by the lack of information on FVIII exposure in non-inhibitor patients and therefore can be compared to results from other studies..

Comparison with other studies

Inhibitor rate in non-severe patients was about three times higher than in PTPs with severe haemophilia A collected in EUHASS: 0.43/100 treatment years (CI 0.30-0.59) in non-severe versus 0.15/100 treatment years (CI 0.10-0.22) in severe haemophilia A. For non-severe haemophilia B, the inhibitor rate was similar at 0.05/100 treatment years (CI 0.001-0.26) compared with 0.04/100 treatment years (CI 0.001-0.20) in PTPs with severe haemophilia B, but is based on the observation of only one inhibitor in each patient group (23). Comparisons with other studies reporting on non-severe haemophilia are hampered by differences in study design. Large cohort studies present the lifetime inhibitor risk as cumulative incidence ranging from 6-13% in non-severe haemophilia A (11-12,14) . For haemophilia B, the UK national registry reported no inhibitors in non-severe haemophilia B (http://www.ukhcdo.org/docs/AnnualReports/2012/), and the American Universal Data Collection database reported a prevalence of 0.33% (30). The largest and most important study on inhibitor development in moderate and mild haemophilia to date, the INSIGHT study, reported on 2711 patients ever exposed to FVIII from 34 centres (12). Treatment was collected as EDs, and lifetime inhibitor risk was calculated according to EDs. In a subset of 1112 patients, 59 inhibitors occurred in 25700 observation years, which would result in an inhibitor rate of 0.23/100 treatment years, if all patients were treated each year, or 0.46/100 treatment years if patients were treated every other year. The latter treatment intensity is more likely to reflect clinical practice, and this inhibitor rate is close to the inhibitor rate observed in the present study. Details on INSIGHT patients who developed inhibitors during 2000-2010 were similar to those observed in EUHASS: inhibitors occurred at a median age of 46 years (P25-P75: 18-65), after 32 EDs (P25-P75: 21-75), including 61% high titre inhibitors. The INSIGHT study included survival analysis according to EDs suggesting that inhibitor risk in non-severe haemophilia continued to increase after 50 EDs. There is an overlap between the INSIGHT and EUHASS studies as 20 centres participated in both during 2.25 years (Oct 2008-Dec 2010). However, the only overlap reported consists of the characteristics of inhibitor patients. The INSIGHT study did not address inhibitor development according to concentrate nor the incidence rate of inhibitors according to 100 treatment years. Rather, it has focused on etiological factors including genetic risk factors(12) and the effects of surgery(31), while others have studied the effects of age on inhibitor risk(11). Unfortunately, these risk factors cannot be studied in the EUHASS

registry, which is focused on detecting the risk of inhibitor development according to different concentrates. Similar to findings in severe haemophilia patients, no difference according to concentrate type nor between plasma derived and recombinant FVIII concentrates was observed.

Clinical relevance

The importance of actively monitoring for inhibitor development in moderate and mild haemophilia is supported by the data presented here: inhibitors in non-severe haemophilia A occur more frequently than in PTPs with severe haemophilia, and continue to develop after 50 EDs. Unfortunately, EUHASS data do not permit assessment of inhibitor development according to age, EDs, or other risk factors. Other studies have shown that older patients, patients undergoing surgery and those with certain mutations have an increased inhibitor risk(11-12,31) . It has been described that at least half of the patients have high titre inhibitors, and clinical problems are caused by the reduced endogenous FVIII activity and increased rates of bleeding events (12,14). Although the power of the present study is limited by low numbers, these results do not give reason to select or avoid any of the products assessed.

The observation that the number of non-severe patients treated is much lower than the number of patients monitored by centres, emphasizes the value of calculating inhibitor risk according to concentrate treatment years. Many mild haemophilia A patients are treated with Desmopressin which does not have an inhibitor risk as the released FVIII is endogenously produced.

Conclusion:

EUHASS is an international multicentre pharmaco-surveillance system covering a continuously growing open population. Further insights into the development of inhibitors in mild and moderate patients will be available in the future.

Table 1. Data analysed and inhibitors observed in non-severe haemophilia patients according to treatment status and diagnosis

Centres included	68/74 (92%)	
Inhibitors included	40/48 (83%)	
Number of patients registered	9832/10940 (90%)	
	Haemophilia A	Haemophilia B
Number of patients registered	7969	1863
Treatment years	8622	2149
Inhibitors observed	39	1

Table 2. Characteristics of inhibitor patients in non-severe haemophilia according to diagnosis

	Haemophilia A median (P25-P75)	Haemophilia B median (P25-P75)
Number	39*	1
Age (yrs)	35.3 (9.3-67.9)	26
Moderate haemophilia	36%	0%
Number of EDs before inhibitor development	38 (20-80)	6
Median 1st titre	4.0 (1.1-12.2)	5
Inhibitors within the first 50 EDs	72%	100%
% high titre within first two measurements	51.3%	100%

*Including 2 inhibitors on Haemate P that were not included in the overall calculation of inhibitor rate due to incomplete data on the number of patients at risk
EDs = exposure days

Table 3. Inhibitor development according to concentrate types and individual recombinant concentrates

	Inhibitors (N)	Treatment years (N)	Inhibitors (N/100 yrs) (95% CI)
Haemophilia A			
Haemophilia A overall	**37**	**8622**	**0.43 (0.30-0.59)**
FVIII rec	34	6546	0.52 (0.36-0.73)
FVIII pd	3*	2076	0.14 (0.03-0.42)
FVIII BHK	12	2993	0.40 (0.21-0.70)
FVIII CHO full	11	2455	0.45 (0.18-0.73)
FVIII CHO BDD	11	1088	1.01 (0.51-1.80)
Advate	9	2335	0.39 (0.18-0.73)
Helixate NexGen	5	1091	0.46 (0.15-1.07)
Kogenate Bayer	7	1902	0.37 (0.15-0.76)
Recombinate	2	121	1.66 (0.20-5.87)
Refacto	3	130	2.30 (0.48-6.58)
Refacto AF	8	958	0.84 (0.36-1.64))
Haemophilia B			
Haemophilia B overall	**1**	**2149**	**0.05 (0.001-0.26)**
FIX pd	0	735	0.00 (0.00-0.50)
FIX rec (Benefix)	1	1414	0.07 (0.00-0.39)

*data for inhibitor development on Haemate P are not included due to incomplete data on the number of patients at risk,

PTPs = previously treated patients

rec = recombinant

pd = plasma derived

BHK = Baby hamster kidney cells

CHO = Chinese hamster ovarian cells

BDD = B-domain deleted

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Authorship:

K Fischer, M Makris, R Lassila, F Peyvandi, G Calizzani, A Gatt, T Lambert and J Windyga conceived and designed the study. M Makris and E Gilman secured funding and managed study procedures (governance and data management). M Makris, K Fischer, and E Gilman coordinated and performed datachecking. K Fischer planned and undertook the statistical analysis, which was independently repeated by A Iorio. All authors performed data interpretation. K Fischer, A Iorio and M Makris drafted the manuscript, which was completed with input from all authors. All the authors approved the final manuscript.

Datacollection was performed by K Fischer, R Lassila, F Peyvandi, A Gatt, T Lambert, J Windyga ,A Iorio, M Makris and all collaborators/centers collaborating in the EUHASS project (separate list)

A list of collaborators to the EUHASS project is shown in the supplementary material.

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Competing interests:.

KF 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.

RL received honoraria for advisory board participation for Novo Nordisk, Pfizer and Sanquin.

FP 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.
TL received honoraria for consultancy, advisory board participation and /or invited educational lectures from Baxter, Bayer, CSL Behring, and Pfizer.
AG, GC and EG reported no competing interests.
JW has acted as a consultant and participated in expert groups for Bayer, Baxter and Novo Nordisk, and has received speakers fees from Bayer, Baxter, CSL Behring, Novo Nordisk, Octapharma, and Pfizer.
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MM 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.