Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Haemophilia (2017), 1–9 DOI: 10.1111/hae.13167

ORIGINAL ARTICLE

Natural history and clinical characteristics of inhibitors in previously treated haemophilia A patients: a case series

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Background: Development of inhibitors is the most serious complication in haemophilia A treatment. The assessment of risk for inhibitor formation in new or modified factor concentrates is traditionally performed in previously treated patients (PTPs). However, evidence on risk factors for and natural history of inhibitors has been generated mostly in previously untreated patients (PUPs). The purpose of this study was to examine cases of *de novo* inhibitors in PTPs reported in the scientific literature and to the EUropean HAemophilia Safety Surveillance (EUHASS) programme, and explore determinants and course of inhibitor development. **Methods:** We used a case series study design and developed a case report form to collect patient level data; including detection, inhibitor course, treatment, factor VIII products used and events that may trigger inhibitor development (surgery, vaccination, immune disorders, malignancy, product switch). **Results:** We identified 19 publications that reported 38 inhibitor cases and 45 cases from 31 EUHASS centres. Individual patient data were collected for 55/83 (66%) inhibitor cases out of 12 330 patients. The median (range) peak inhibitor titre was 4.4 (0.5–135.0), the proportion of transient inhibitors was 33% and only two cases of 12 undergoing immune tolerance induction failed this treatment. In the two months before inhibitor development, surgery was reported in nine (22%) cases, and high intensity treatment periods reported in seven (17%) cases. **Conclusions:** By studying the largest cohort of inhibitor development in PTPs assembled to date, we showed that inhibitor development in PTPs, is on average, a milder event than in PUPs.

Keywords: factor VIII inhibitors, haemophilia A, previously treated patients

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Accepted after revision 1 December 2016

Background

The development of inhibitors, or neutralizing alloantibodies, continues to be the most serious challenge in the treatment of haemophilia A. High titre inhibitors interfere with factor VIII (FVIII) replacement therapy, which often becomes completely ineffective, and are associated with high morbidity and mortality [1]. The highest risk of developing inhibitors in persons with haemophilia A occurs within the first 50 exposure days (ED) to FVIII; a substantially lower risk has been observed in patients treated for more than 150 ED, who are commonly called previously treated patients (PTPs) [2]. Indeed, the rate of inhibitor development in PTPs has been estimated to be about three events (95% CI = 2–4) per thousand patient years [3]. Due to this very low event rate in PTPs, our knowledge about risk factors for inhibitor development is mostly based on studies in previously untreated patients (PUPs), variably defined as patients with <50 to 150 ED [4,5], who are mostly young children with severe haemophilia A. On the other hand, current International Society on Thrombosis and Haemostasis and European Medicines Agency/Food and Drug Administration recommendations for assessment of the immunogenicity of new clotting factor concentrates indicate PTPs as the most suitable population [4,6–8]. The concept behind this recommendation is that persons with haemophilia A previously tolerized to FVIII will maintain tolerance to sufficiently similar new molecules, while they would react to those presenting important neo-antigens.

For these reasons, many published reports presenting rates of inhibitors in PTPs are available only as part of phase III or IV studies, or as clinical observation reports. The main focus of these publications is to report, discuss and sometimes even compare (though comparisons are, of course, largely underpowered) rate of inhibitors with different molecules [9–11]. Much less is known about the natural history of inhibitors development in PTPs or about the triggering risk factors at play, which would be clinically important considering that the life expectancy of patients with haemophilia has doubled since the 1960s, from less than 30 to more than 60 years of age [12], and there is mounting evidence suggesting a higher incidence of inhibitors in PTPs aged 60–69 years [13,14].

To respond to this unmet clinical need, we have examined all cases of new inhibitors in PTPs identified from a systematic review of the literature and an international haemophilia registry.

Methods

We have designed the study as a case series, a design that has been recommended for studying rare adverse events. Indeed, this study design allows us to explore the characteristics of patients over a spectrum of cases, drawing loose inference from the underlying cohort and internal comparisons among cases with different characteristics. The design has high feasibility and is not resource intensive, and can be used as the first exploratory step in planning more robust future studies [15,16].

Identification of inhibitor cases

Systematic review. Methods for the systematic review have been published elsewhere [3].

Haemophilia adverse events surveillance system. The EUropean HAemophilia Safety Surveillance System (EUHASS) scheme collects information on adverse events related to haemophilia treatment, including the development of new inhibitors. For each inhibitor event, information is reported about the patient (age, gender, diagnosis, factor level) and the event (date, factor concentrate, additional blood products, assay, inhibitor levels, positive test cut-off). At the time of the study, EUHASS was in its fourth year. We identified cases of new inhibitors reported to EUHASS.

Case report form

We drafted the case report form (CRF) based on current knowledge of development of inhibitors. The CRF was intended to gather additional data that was not often contained in published reports. The draft was circulated for review and feedback to the authors of the publications included in the study and the European Haemophilia Network (EUHANET) network coordinators. The CRF was revised and finalized based on reviewers' comments (Table S1).

Data collection

We took a multi-stage approach for contacting study authors and directors of haemophilia treatment centres participating in the EUHASS network to complete the CRF for each PTP with a new inhibitor. We included in the CRF all the known risk factors for inhibitor development in PUPs, as detailed in the Table 1 (see also Table S1). All respondents were invited to co-author the study report.

Definitions

Haemophilia was defined as severe for plasma FVIII levels of <0.01 IU mL^{-1}; moderate haemophilia, for 0.01 to 0.05 IU mL^{-1} of FVIII; and mild haemophilia, for 0.06 to 0.40 IU mL^{-1} of FVIII. Previously treated persons (PTPs) with haemophilia were defined as patients treated for 50 or more ED, due to the lack of an accepted international definition for PTPs and variability in the definitions currently used to identify PUPs.

Table 1. Risk factors for inhibitor formation.

Modifiable: treatment	Factor VIII (FVIII) concentrate Regimen (prophylaxis or on demand, dosage, interval)
Modifiable: trigger events or inflammatory responses	Age of first exposure to FVIII concentrate Surgery Vaccination Intense FVIII treatment periods Infection or immunologic challenge
Non-modifiable: genetics	Switch in FVIII concentrate Ethnicity Family history of inhibitors Genotype FVIII mutation

However, we planned to report separately the number of cases falling into the following categories: 50 to 74, 75 to 149 and ≥150 ED. High responders were defined as patients with a peak titre >5.0 Bethesda Units (BU) mL^{-1} at diagnosis. Transient inhibitor was defined as an inhibitor that spontaneously resolved within six months without change in treatment regimen, i.e. without immune tolerance induction (ITI). As to the test used to diagnose inhibitors we accepted methods of Bethesda or its Nijmegen modification, and thresholds for negative values as reported by the authors or case contributors and the available information. Intense FVIII treatment period was as reported by the individual investigators who completed the CRF. Our guidance was that any treatment of 50 U kg^{-1} or more for three or more consecutive days would constitute an intense treatment period.

Statistical analysis

We considered each of the cases for which we were provided the CRF as one unit of a case series. We assumed data were missing at random both for inhibitors cases for which we did not get a CRF and for missing information in an incomplete CRF was incomplete. Consequently, we described our cases series by calculating central tendencies as mean and standard deviation or median and range, or calculating proportions of cases with specific characteristics as appropriate. For each descriptive measure, we reported the actual sample size.

Results

The Preferred Reporting Items for Systematic Reviews (PRISMA) flow diagram provided the details of the case identification and data-gathering process (Fig. 1).

Systematic review

Detailed results of the systematic review are published elsewhere [3]. In summary, we identified 19 publications that reported 38 new inhibitors in PTPs with haemophilia A.

Of the 38 identified inhibitors, we collected individual patient data for 29 (76%) inhibitor cases overall. The source population for the 29 inhibitors was 4443 patients with haemophilia A (as calculated by summing up the number of patients included in the reports from which the 29 cases were obtained); thus, the inhibitor rate was 6.5 per 1000 patients (29/4443). The data originated specifically from:

1. 13 (34%) CRFs completed by study authors for cases reported in nine publications [17–25].
2. 16 (42%) CRFs completed by extracting patient level information available from eight published reports [26–33].

For nine inhibitors (24%) reported in three publications [26,34,35], data extraction was not possible because the relevant publications included only aggregated summary data and the study investigators were unable to provide individual level data. One inhibitor was also reported to EUHASS.

Haemophilia adverse events surveillance systems

There were 45 cases of new inhibitors in PTPs with severe haemophilia A reported to EUHASS in 31 of 75 participating European treatment centres. Nineteen (61%) centres reporting inhibitors in the study provided CRF for their 26 cases (58%; Fig. 1). The source population for the 26 inhibitors in EUHASS was estimated at 7887 (based on 31 551 patient years of follow-up reported by the centres observing the 26 inhibitor cases – data obtained directly from the EUHASS registry); thus, the inhibitor rate was 1.14 per 1000 patient years. An approximate estimate comparable to the one calculated above from the published literature (based on the sum of the patients enrolled in each study) would be 3.3 per 1000 patients (26/7887), not taking time into account.

Patient characteristics

In total, 55 cases were identified (29 in published literature, 26 reported to EUHASS). Severity of haemophilia A was available for 54 patients with inhibitors: the majority (48 of 54) had severe haemophilia, four patients had moderate haemophilia and two patients had mild haemophilia. Thirty-six patients were reported to be White or Caucasian; one patient was Asian and another was Black. Information about ethnicity was missing for the other 17 patients.

Inhibitor characteristics

The inhibitor cases were diagnosed from 1998 (in the literature) to 2014 (reported to EUHASS). Forty-one of 54 cases were diagnosed using the Bethesda assay,

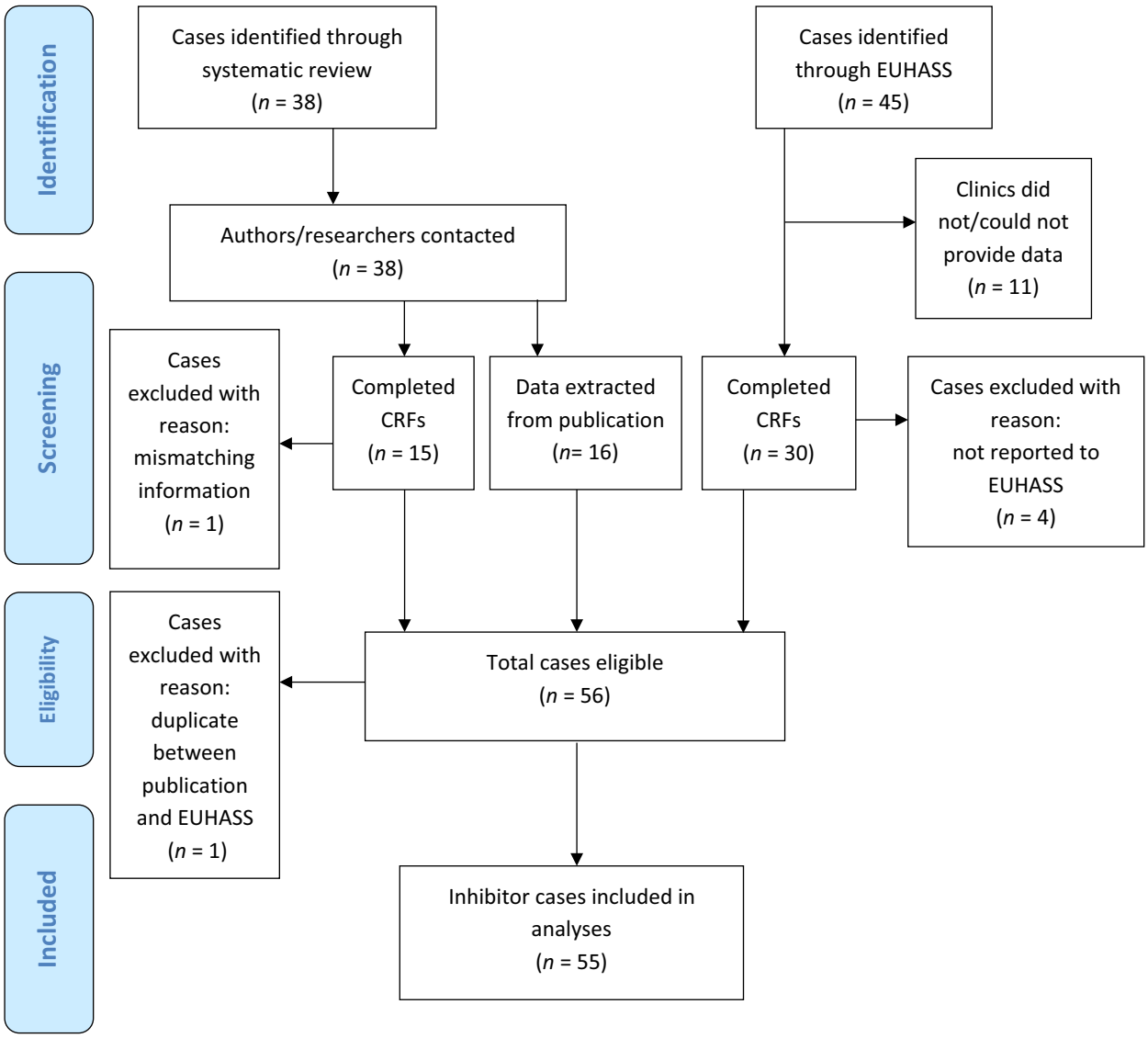

Fig. 1. Preferred Reporting Items for Systematic Reviews flow diagram. CRF, case report form; EUHASS, EUropean HAemophilia Safety Surveillance.

while for the remaining, the Nijmegen modification or a combination of the two tests was used. Forty of 43 cases used a cut-off for inhibitor of 0.6 BU mL^{-1} or lower, and three used a cut-off of 1.0 BU mL^{-1}.

ED at time of inhibitor detection was reported for 49 patients (of which, 43 had severe haemophilia A). Twenty-seven cases (25 with severe haemophilia A) had 150 ED or more. Six patients were reported as PTPs by the haemophilia treatment centre to EUHASS ($n = 2$) or by the study authors in their publication ($n = 4$), but the numbers of EDs were not provided. Seventeen (15 with severe haemophilia) had reached 75 to 149 ED. Five patients had between 50 and 74 ED; three of these patients had severe haemophilia A, one had mild haemophilia A and the other patient's severity was not reported in the literature.

There were 24 high responders with severe haemophilia A. The peak titre levels for these patients ranged from 5.0 to 135 BU mL^{-1} (mean = 30.9). Fourteen of the cases were tested because of clinical signs and 10 were clinically significant following diagnosis. The last known titre level of 10 high responders was more than 1 BU mL^{-1}. Further details regarding the inhibitors are reported in Tables 2 and 3.

Frequency of occurrence of known risk factors for inhibitors development

The age of the patient at first FVIII exposure was known and reported for 31 patients; age at first exposure ranged from six weeks to 55 years (mean = 12.7;

Table 2. Inhibitor characteristics of *all* patients by data source.

Characteristic	*N*	Mean (SD)	Median	Range
Age at inhibitor diagnosis (years)				
Published literature	23	44 (18)	50	2–67
EUHASS registry	26	29 (18)	32	1.1–72
All	49	36 (19)	35	1.1–72
Exposure days (ED) at diagnosis[†]				
Published literature	25	150 (76)	120	50–363
EUHASS registry	24	280 (372)	150	55–1850
All	49	215 (273)	150	50–1850
Titre level at first assessment, BU mL^{-1}				
Published literature	28	4.4 (8.4)	1.2	0.4–34.0
EUHASS registry	26	9.0 (14.2)	3.1	0.6–54.0
All	54	6.6 (11.6)	1.6	0.4–54.0
Peak titre level, BU mL^{-1}				
Published literature	25	11.1 (18.6)	2.4	0.5–75.0
EUHASS registry	26	20.0 (30.9)	7.5	0.8–135.0
All	51	15.7 (25.8)	4.4	0.5–135.0
Last known titre level, BU mL^{-1}				
Published literature	15	1.5 (2.6)	0.4	0.0–10.4
EUHASS registry	26	3.4 (8.6)	0.5	0.0–41.0
All	41	2.7 (7.0)	0.4	0.0–41.0
Patient follow-up after inhibitor diagnosis, months[‡]				
Published literature	10	62 (59)	40.5	1–143
EUHASS registry	22	43.6 (42)	29.5	1–166
All	32	49.3 (48.6)	29.5	1–166

N, number of patients with available data; SD, standard deviation; BU mL^{-1}, Bethesda Units per millilitre; EUHASS, EUropean HAemophilia Safety Surveillance.
[†]Five patients had EDs of 50, 55, 59, 65 and 68 EDs at time of inhibitor detection; 17 patients had 75 to 143 EDs, and 27 had ≥150 ED; ED were not reported for six patients.
[‡]Four patients followed up for less than 1 year.

Table 3. Inhibitor characteristics of *severe* haemophilia A patients ($n = 48$).

Characteristics	*N*	Mean (SD)	Median	Range
Age at inhibitor diagnosis, years	43	34 (19)	36	1.1–72.0
Exposure days (ED) at diagnosis[†]	43	227 (287)	150	55–1850
Titre level at first assessment, BU mL^{-1}	48	6.8 (12)	1.6	0.39–54.0
Peak titre level, BU mL^{-1}	47	16.8 (26.3)	4.8	0.7–135.0
Last known titre level, BU mL^{-1}	38	2.9 (7.1)	0.5	0.0–41.0
Patient follow-up, months	30	50 (49)	30	1–166

N, number of patients with available data; SD, standard deviation; BU mL^{-1}, Bethesda Units per millilitre.
[†]Three patients with EDs of 55, 59 and 65 EDs at time of inhibitor detection; 15 patients had 75 to 143 EDs and 25 had 150 ED or more; ED was not reported for five patients.

SD = 14.7). Eight PTPs had a known family history of inhibitors. Information about the factor FVIII product used at inhibitor detection was available for 54 patients with inhibitors (Table 4).

During their lifetime, 14 patients had a surgical procedure, 38 had switched FVIII products, 10 were vaccinated, five had an immune disorder, two had a malignancy and 14 had a period of intense FVIII treatment (eight of these cases was associated with surgery; Table S2).

Data on risk factors during the two months prior to inhibitor detection was provided for 41 cases. Eighteen patients had at least one risk factor during that time period; five patients had two (three had surgery and intense FVIII treatment, one had surgery and switched treatment, and another was vaccinated and diagnosed with malignancy) and two patients experienced three risk factors (one had surgery, intense treatment and malignancy; another had surgery, intense treatment and switched product).

Nine patients (of which, four had ≥150 ED) had surgery. Six patients had severe haemophilia and had the following procedures: surgery for urinary cancer on the same day of inhibitor detection; total knee surgery nine days earlier; knee synovectomy on the same day; unspecified surgery 14 days earlier; dental surgery 21 days earlier; and prostatic adenoma and bladder polyps resection 43 days earlier. One patient had the inhibitor diagnosed on the day of surgery, which was complicated by sepsis; he had switched concentrate one month before surgery, and died on the day of surgery. The following details were reported for the other three non-severe PTPs: peripheral arterial occlusive disease bypass operation five days earlier; and prostate biopsies 20 days earlier (no details provided for one patient). Four severe PTPs and one with unknown severity switched FVIII (mean = 26 days, range = 1–60).

Two of these patients switched products 22 and 30 days prior to surgery (also counted above). One severe PTP was vaccinated, and one patient was diagnosed with an allergic reaction (urticaria). Three patients received the following diagnoses of malignancy: prostate cancer, lymphoproliferative disorder and mesothelioma. Only the patient with prostate cancer also had surgery and was counted above. Seven patients had intense treatment with FVIII (two had severe haemophilia A). The intense treatment was associated with surgery for five patients. One patient had severe ankle traumatic haemarthrosis and the other patient had a hip bleed following physical exercise.

FVIII genotype was reported for 26 patients, of which 24 had severe haemophilia A (Table 5).

Table 4. FVIII use at inhibitor detection.

Characteristic at inhibitor development	All	Severe only	150 ED or more
Product used			
Recombinant[†], all	43[‡]/54	37/48	21/27
Plasma-derived, all	11[§]/54	11/48	6/27
Treatment indication			
On demand	20/38	19/33	13/26
Prophylaxis	14/38)	12/33	8/26
Surgical prophylaxis	4/38	2/33	2/26

[†]Top recombinant products: Kogenate ($n = 11$), Refacto AF/Xyntha ($n = 11$), Advate ($n = 4$), Helixate-Nexgen ($n = 3$).
[‡]Of the 43 patients, 14 were previously on another recombinant product, 10 were on a plasma-derived product and one patient switched from another unspecified product.
[§]Of these 11 patients, five were previously on a different plasma-derived product, two were on a recombinant product, two never switched their product, and two switched from other products, for which there were no available details.

Clinical course

Sixteen of 48 inhibitors were reported as spontaneously disappearing after six months without treatment. This group included the four patients with moderate haemophilia and 12 patients with severe haemophilia. For these transient inhibitor cases, age varied from 2 to 61 years and peak titre level ranged from 0.5 to 30 BU mL^{-1}. One inhibitor spontaneously resolved after 1 year. Clinical events following the diagnosis of the inhibitor were reported for 17 of 40 patients, and included haemorrhage, decreased recovery, increased bleeding rate and haemarthrosis.

Twenty-one of 40 patients required a bypassing agent (recombinant factor VIIa or activated prothrombin complex concentrates). Patient ages spanned from 1 to 72 years (mean = 38). Peak titres ranged from 2.0 to 135 BU mL^{-1}; 16 patients were high responders. Twenty had severe haemophilia and one had mild haemophilia.

Twelve of 40 patients were treated with ITI. All had severe haemophilia A. Patients were aged 1 to 48 years (mean = 28), and all but the youngest patient had history of 150 ED or more. Nine patients were high responders with peak titres ranging from 7.0 to 135 BU mL^{-1}. For 10 of these 12 cases, ITI was successful.

Of the 55 inhibitor patients, 26 were still alive. Of the 26 inhibitor patients reported to EUHASS, 23 were alive and still followed in the reporting centre. Data on live status for cases reported in the literature were available for only six patients, three of which were reported as alive and being followed by the centre.

Table 5. Reported details of known FVIII genotype for 26 patients.

FVIII genotype details	Severe only (*n*)	Non-severe (*n*)
Intron 22 inversion	11	0
Missense mutations, without further specifications	2	0
c.971>G, pTrp33Gly	1	0
Small inversion A 6960 6961	1	0
Stop codon in exon 16	1	0
Stop codon 1198 in exon 14	1	0
p.Arg2169His	0	1
p.Gly470Arg	0	1
p.ArgR1997TrpW	1	0
p. Val 253 Phe	1	0
pR1997W	1	0
p.Asn1460LysfsX2 (insertion of nucleotide A in a stretch of 9 A in exon 14; stop codon)	1	0
Arg3Gly	1	0
Deletion R1696 (A3 domain)	1	0
Complex gene rearrangement – not typical IVS 22	1	0

Discussion

This study reviewed a cohort of 55 cases of inhibitors which developed among approximately 12 000 PTPs with haemophilia A. To the best of our knowledge, this is the largest ever cohort of inhibitor cases studied. Using a standardized CRF, we have been able to analyse the characteristics of these patients, the clinical course of their inhibitors and the role of risk factors. Inhibitor development is a complex multifactorial process. A number of risk factors have been identified in PUPs, including non-modifiable risk factors, specifically related to genetics, and modifiable or environmental risks factors [36]. Many previously published papers assessed the inhibitor rate in PTPs enrolled in phase III or phase IV studies [7,22,24,25,37], or presented meta-analyses of such studies [3,11,38]. The main focus of these publications was to report, discuss and sometimes compare rate of inhibitors observed with specific molecules, to define their immunogenicity. Almost no attempt has been made before this study to explore the natural history of inhibitor development in PTPs or the triggering risk factors at play.

In this study, most inhibitors developing in PTPs were of low titre, and disappeared spontaneously or after a course of ITI. The risk conditions more frequently found shortly before inhibitor development were surgery and/or periods of intense treatment with FVIII. Other conditions considered candidate risk factors for inhibitor development in PUPs (product switching, vaccination, immune disorders and malignancy) were found less frequently. We believe that the information about the frequency of occurrence of these characteristics is new, clinically relevant and confident; it will trigger new research to explore causality.

The only risk factor that has been explored to some extent has been switching factor concentrate, a concept closely related to molecule immunogenicity. Indeed, some reports have discussed whether switching from one concentrate to another (regardless of the specific products) increases the risk of inhibitor development in PTPs, as a result of molecular differences [6,9,10,39,40]. However, few of the studies were comparative in nature and, most importantly, none took into account other risk factors concurrent with factor concentrate switching mostly due to insufficient power [40]. By contrast, in the analysis of our cohort, we considered factor concentrate switching as one of several candidate risk factors, and we rigorously adopted a standard and narrow time window around the switch itself; when doing so, switching did not appear to have any important role. Indeed, our analysis confirmed that switching in the two months prior to development of an inhibitor occurred only in five of 52 (10%) cases, of which only three (6%) had factor switching as a single candidate risk factor (the other two patients also had surgery during the two-month time period).

One compelling reason for interest in inhibitor development in PTPs stems from the evidence

suggesting higher incidence in patients aged 60–69 years [13,14]. This is very important considering the increasing life expectancy of patients with haemophilia [12]. One might observe that only six of our cases fell in the above age range; the average age at inhibitor development in our case series was 36 years of age. This might cast doubts about the applicability of our findings to an older population; however, it must be noted that in our case series, mean (36 years) and median (35 years) almost overlapped, and the age range spanned from 1 to 72 years, suggesting that development of inhibitors in PTPs is a random event, not correlated with age. The average age measured in our study likely overlaps with the average age of the underlying population at risk.

While the major strength of our study is the relatively large number of occurrences of a very rare event, its main limitation is the absence of a control group. We adopted, for convenience and economy, a case series design. This design has been recommended for studying rare adverse events and combines the power and simplicity of the cohort method and the economy of the case–control method, while reducing confounding caused by factors that vary between participants. This design also makes it possible to provide richer and more comprehensive information than is usually gathered with randomized controlled trials [15]. We expect that the novelty of the evidence we have produced will prompt the leveraging of resources and willingness to participate in a future matched case–control study, which is needed to confirm or deny the causality of the association we have suggested. We strongly recommend that performing such a study is seriously considered by organizations in the field and we will work with the EUHASS network to assess feasibility of a nested case–control study within their data collection framework. Other possible limitations of our study are the incompleteness of the case series and recall or detection biases. We have been able to gather data for 55 out of 83 cases (66%) reported in the literature and to EUHASS. While we acknowledge that the incompleteness of the case series might introduce bias, we have no specific reason to suspect that missing information is not random. Indeed, the authors and treatment centres tended to report on either all or none of their patients. However, we found that the rate of inhibitors was about twice as high in the literature series as compared to the EUHASS data collection (6.5 vs. 3.3 per 1000 patients). This difference can be explained by either overreporting due to recall bias in the literature series or underreporting of missed data in the EUHASS data collection. The former can introduce bias towards more or less severe cases being reported, the latter likely missing milder cases. In addition, the occurrence of events like surgery or need for intense treatment may have prompted more frequent inhibitor testing, thus increasing the chance of inhibitor detection and introducing potential bias. Finally, different thresholds for diagnosis of an inhibitor (Table S3) and the process itself of estimating the denominator could be responsible for the observed difference. On average, we consider our estimates quite conservative, and a more efficient data collection would possibly show an even less severe impact of inhibitors in their natural history in PTPs. In regard to inhibitor testing, a minor limitation would also be the non-standardization of the clinical and laboratory cut-off for inhibitor diagnosis (Table S3); however, this is less relevant when the inhibitors of interest are clinically significant. Finally, we could not explore the possible role of ethnicity as a risk factor for insufficiency of data and we did not collect information about the success/failure criteria for ITI or its duration.

Conclusions

The development of inhibitors in PTPs is a rare event, and we have now shown that it is usually milder than one might have predicted. Of course, each individual case deserves full support and care, and each case may be perceived as extremely severe for the patient, family and physicians experiencing the inhibitor. However, on a broader population perspective, the risk of development of inhibitors in PTPs might not be considered as relevant information for decisions about individual product switches or tendering processes. Indeed, the benefits from the availability of new or cheaper products might outweigh the risk and impact of inhibitor development in PTPs.

Acknowledgements

We thank the following people for providing data for the study: Dr, Prasad Mathew from Albuquerque, USA; Dr. Jenny Goudemand from Lille, France; Dr. Sylvia Reitter-Pfoertner from Vienna, Austria; Dr. Gianna F. Rivolta from Parma, Italy; Dr. Vadim Romanov from California, USA (at the time of data analysis); Dr. Bülent Zülfikar from Istanbul, Turkey.

Author contributions

AI designed the study and wrote the first draft of the paper. AMB contributed to the study design, collected and analysed the data, and co-wrote the first draft of the paper. The remaining authors contributed by providing original data and participated in interpretation of the results. All the authors approved the final version of the manuscript.

Funding

This study was supported by two independent unrestricted research grants: a 'Care until Cure' peer reviewed research grant, awarded in 2013 to AMB by the Canadian Hemophilia Society (CHS) supported the collection of inhibitor data reported in the literature; a Pfizer Investigator-Initiated Research grant awarded in 2014 to AI supported the collection of data reported to EUHASS.

Disclosures

Ethics approval and consent to participate: The study protocol was waived approval by the Hamilton Integrated Research Ethics Board. We recommended that EUHASS centres seek local ethical clearance.

Consent for Publication: Not applicable.

Availability of data and material: The dataset generated and analysed during this study is available from the corresponding author on reasonable request.

Competing interests: AI has received research funds as Principal Investigator from Bayer, Baxalta, Biogen Idec, NovoNordisk, Pfizer and as consultant from Bayer, NovoNordisk. All funds were paid to McMaster University and none received as personal honorarium. MM has acted as consultant to CSL Behring and NovoNordisk. He took part in an advisory panel organized by BPL and gave lectures for Baxter, Bayer, Biogen Idec, Biotest, Octapharma, Pfizer and SOBI. He received travel support from Baxter and Bayer. MS participated in clinical trials funded by Biotest, Baxter, Bayer, Novo Nordisk and CSL Behring.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Case report form used for data collection.

Table S2. Reported risk factors (for inhibitor formation) in PTPs with inhibitors.

Table S3. Methods used for detecting inhibitors.