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Trends in Treatment of Severe Haemophilia and Impact on Inhibitor Assessment by the EUHASS Registry

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Keywords: antibodies | emicizumab | factor VIII | haemophilia | inhibitor | neutralising | PTP | PUP

ABSTRACT

Background: The last 15 years have seen new extended half-life (EHL) recombinant FVIII/IX concentrates and nonreplacement therapy for haemophilia A (emicizumab) introduced in Europe. These changes affect FVIII/IX exposure in previously untreated patients (PUPs) and previously treated patients (PTPs) with severe haemophilia A and B (SHA and SHB) and may modify inhibitor development and/or detection.

Aim: To report trends in treatment for severe haemophilia and concomitant changes in inhibitor incidence.

Methods: Between 2008 and 2022, 97 centres reported inhibitor development against FVIII/IX concentrates to the European Haemophilia Safety Surveillance System (EUHASS). Inhibitors were reported quarterly, and PUPs without inhibitor development annually. Cumulative inhibitor incidences (95% confidence intervals [CI]) were calculated for PUPs and incidence rates/1000 years (CI) for PTPs.

Results: By 2022, SHA-PUPs ($n = 1574$) received emicizumab (44%), SHL-rFVIII (21.5%), pdFVIII (17.5%) and EHL-rFVIII (17%). SHB-PUPs ($n = 236$) received EHL-rFIX (79%) and SHL-rFIX (21%). SHA-PTPs (68,772 years) received EHL-rFVIII (31%), SHL-rFVIII (28%), emicizumab (25%), and pdFVIII (15%). SHB PTPs (11,185 years) received EHL-rFIX (69%), pdFIX (15%) and SHL-rFIX (15%). Observed Inhibitor incidence in SHA-PUPs decreased from 24% before 2016 to 6% in 2022 ($p < 0.001$), and potentially in SHB-PUPs too (from 9% to 3%; $p = 0.066$), but remained stable in SHA/SHB PTPs.

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Conclusion: In 2022, 44% of SHA-PUPs and 25% of SHA-PTPs received emicizumab prophylaxis. Concomitantly, observed inhibitor incidence reduced to 6% in SHA-PUPs. In SHB, EHL-rFIX treatment increased to 79% in SHB-PUPs and 69% in SHB-PTPs. Assessing inhibitor incidence for new concentrates is likely to be hampered by novel treatments causing delayed exposure to FVIII/FIX.

1 | Introduction

Prophylactic replacement therapy with intravenous clotting factor concentrates (CFCs) to prevent bleeding and subsequent arthropathy has been the cornerstone of treatment of children and adults with severe haemophilia since the 1970s–1980s [1]. Over the last decade, many new treatment modalities have been introduced and more are under development, including the first gene therapies.

For haemophilia A, the development of extended half-life recombinant FVIII (EHL-rFVIII) with half-life extension of around 40% resulted in the possibility of less frequent prophylactic infusions for some patients, albeit many children still need intravenous infusions every 2–4 days to achieve effective prophylaxis [2]. Since the first publication on emicizumab in 2016, the possibility of an effective prophylaxis without the burden of venous access has been especially appealing for infants and toddlers with severe haemophilia A (SHA) [3, 4]. Following favorable reports on its efficacy and safety in adults and children with and without inhibitors, emicizumab has become available in many European countries [5]. Concomitantly, emicizumab is increasingly used for primary prophylaxis in previously untreated patients (PUPs) with SHA, and consequently the exposure to FVIII is reduced and/or postponed in these infants [5, 6].

For severe haemophilia B (SHB), the development of EHL-rFIX concentrates with a more significant extension of FIX half-life of 3–4 times, has allowed for effective prophylaxis with once weekly or even less frequent infusions [2].

Gene therapy was developed first for haemophilia B, but is now approved for adults with both SHA and SHB in the US and Europe [7–9].

Other forms of nonreplacement therapy are rebalancing agents focused on inhibiting tissue factor pathway inhibitor (TFPI) (Concizumab) [10, 11] or antithrombin (Fitusiran) [12–14]. These can be used for prophylaxis in both haemophilia A and B, independent of inhibitor status. Concizumab was recently approved in Canada for haemophilia B patients with an inhibitor and has been submitted for approval in the US and Europe [15].

For all patients on nonreplacement therapies, treatment with CFCs will still be needed in case of acute bleeding or major surgery. Concomitantly, the development of neutralising FVIII/IX antibodies (inhibitors) continues to interfere with treatment. Inhibitor monitoring is most efficiently reported in national and international registries, including the prospective European Haemophilia Safety Surveillance (EUHASS) registry, which started in 2008 [16]. In this changing treatment landscape, it is hypothesised that different treatment patterns may modify treatment intensity and subsequent inhibitor development in patients with severe haemophilia.

Using data from the first 14 years of EUHASS, the present report aims to assess the changes in the treatment modalities used for severe haemophilia in Europe and report concomitant evolution in the reported inhibitor development against FVIII/FIX concentrates.

2 | Methods

The present analysis included data collected during 14 years from 1 October 2008 to 1 January 2023, from 97 European centres participating in the EUHASS study. A list of participating centres is provided in the Supplementary Material. The design of the EUHASS study was described previously [16, 17]. Briefly, the number of PUPs reaching 50 exposure days (EDs) without inhibitor development, as well as the number of severe haemophilia patients with more than 50 EDs (previously treated patients [PTPs]) according to concentrate were reported annually by each participating centre. Concomitantly, the occurrence of new inhibitors was reported quarterly, including age, number of EDs before inhibitor development, and concentrate used prior to inhibitor development. EDs were recorded up to 1000 EDs and coded as >999 EDs for patients with 1000 EDs or more. Inhibitors were defined by two subsequent positive tests according to the local laboratory.

Prior to study entry, all centres obtained approval from their institutional review boards. Individual informed consent was not obtained as all data were collected at group level or coded (inhibitor data).

3 | Statistics

Data were analysed separately for haemophilia A and B, as well as for PUPs defined as those with up to 50 EDs to CFCs and PTPs defined as those with >50 EDs to CFCs.

For each group, and each year, the proportion of patients on plasma-derived concentrates (pd FVIII/FIX), standard half-life recombinant concentrates (SHL-rFVIII/FIX), EHL recombinant concentrates (EHL-rFVIII/FIX), or nonreplacement therapy (for haemophilia A only, emicizumab) was calculated.

Inhibitor incidence was expressed as a cumulative incidence with 95% confidence intervals (CI) for PUPs. For PTPs inhibitor development was expressed as incidence rates/1000 treatment years (IR) with CI, for each observation year for haemophilia

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A, and for two periods of 7 years (i.e., before vs. after 2016) for haemophilia B due to lower patient numbers.

Data were analysed separately for PUPs and PTPs with haemophilia A and B, respectively. Types of concentrates (pd FVIII/FIX, SHL-rFVIII/FIX, or EHL-rFVIII/FIX) and periods before 2016 and since 2016 were compared. Participants in gene therapy studies were not included in the analyses. Proportions were compared using Chi Square tests, rates were compared using incidence rate ratios (IRR) with their CI. IRR were calculated using Medcalc [18]. Descriptive statistics were performed using SPSS 29.0.

4 | Results

4.1 | PUPs With Severe Haemophilia A

In total, data on 1574 PUPs were collected, including 743 before 2016 and 831 since 2016 (Table 1). The number of PUPs reported showed little variation over time (data available on request). The treatment used, however, showed clear changes provided Figure 1. The first treatment with EHL-rFVIII was recorded in 2015, with a steep increase in the use of EHL-rFVIII from 2017 onwards, eventually resulting in 17.0% of PUPs treated with EHL-rFVIII in 2022. Concomitant with the introduction of emicizumab in EUHASS in 2017, the use of SHL-rFVIII declined whilst the use of pdFVIII remained quite stable. In 2022, emicizumab was the most frequently used prophylactic treatment used in 44%, while SHL-rFVIII was used in 21% and pdFVIII was used in 17% of PUPs.

FVIII inhibitor development in PUPs is shown in Figure 2 and Table 1. While FVIII inhibitor incidences in PUPs were stable at an average of 24% during the period of 2009–2015, a steep decline occurred in the number of inhibitors which were reported to EUHASS after 2016, down to 6% in 2022. When comparing FVIII inhibitor development over the period of 2009–2015 (24%) to the period of 2016–2022 (16%), this difference was highly significant (p value <0.001). Inhibitor development on EHL-rFVIII (20/122; 16%; CI 10%–24%) was not significantly lower than on pdFVIII and SHL-rFVIII combined (22%; CI 20%–24%, p value 0.165) and could not explain the decline in inhibitor incidence. Inhibitor development was still reduced when considering SHA-PUPs treated with FVIII concentrates only, from 24% (CI 21–28) before 2016, to 10% (CI 4–21; p 0.014) in 2022.

4.2 | PUPs With Severe Haemophilia B

In total, data on 236 PUPs with SHB were collected, with stable numbers over time: 115 reported before 2016, and 121 reported since 2016 (Table 1). The trends of the treatment over time are shown in Figure 3. The first use of EHL-rFIX was reported in 2017, and since then, the use of EHL-rFIX increased to 79% in 2022, with the remaining 21% of patients receiving SHL-rFIX without any PUPs on pdFIX. Concomitantly, the inhibitor development appeared slightly reduced from 9% (CI 4%–15%) before 2016, to 3% (CI 2%–8%) since 2016 (p value 0.066). This change could not solely be attributed to a difference in inhibitor development according to concentrate, since the inhibitor development on EHL-rFIX (2/65, 3%; CI 0.4-11%) was similar to the inhibitor development on pdFIX and SHL-rFIX combined (12/171, 7%; CI 4–12%, p value 0.223).

4.3 | PTPs With Severe Haemophilia A

For PTPs, the number of patients treated according to the concentrate was reported annually, resulting in a total of 74,512 reported treatment years, divided almost equally over the period before 2016 (36,270 years) and since 2016 (38,242 years) (Table 1). For this group, the first use of EHL-rFVIII was reported in 2016, and the first use of emicizumab in 2017. The trends in treatment used over time are shown in Figure 4. Before 2016, 29% of patients used pdFVIII and 71% used SHL-rFVIII. Since 2016, almost half of the patients switched to emicizumab or EHL-rFVIII, and in 2022, 28% used SHL-rFVIII, 32% used EHL-rFVIII, 15% used pdFVIII, and 26% used emicizumab. The inhibitor development remained stable at 1.0/1000 years (CI 0.7–1.4) before 2016 compared to 0.7/1000 years (CI 0.49–1.06) since 2016 (IRR 1.4; CI 0.9–2.4, p value 0.151).

4.4 | PTPs With Severe Haemophilia B

For PTPs with SHB, a total of 12,059 treatment years were reported, including 5797 years before 2016 and 6262 years since 2016 (Table 1). Changes in the treatment trends over time are shown in Figure 5. The first use of EHL-rFIX was reported in 2016; no other nonreplacement therapies were recorded for haemophilia B patients. Before 2016, 37% of patients used pdFIX and the remaining 62% used SHL-rFIX. After its introduction, the use of EHL-rFIX increased compared to other concentrates, eventually resulting in 70% on EHL-rFIX, and 15% on both SHL-rFIX and pdFIX in 2022. The inhibitor development was very rare, and the rates remained stable at 0.2/1000 years (CI 0–1.0) before 2016 and 0.5/1000 years (CI 0.1–1.4), resulting in an IRR of 0.4 (CI 0–4.5; p value 0.415).

5 | Discussion

The EUHASS registry showed a progressive uptake of new treatments since 2015 in 1574 PUPs of both SHA and 236 SHB, as well as in the 68,772 treatment years in PTPs of both SHA and the 11,185 treatment years in SHB. For SHA, the uptake was most noticeable for emicizumab, up to 44% of PUPs and 26% of PTPs in 2022, while EHL-rFVIII was used in 17% and 32%, respectively. For SHB, the uptake of EHL-rFIX was most noticeable, which was used by 79% of PUPs and 70% of PTPs in 2022, while none of PUPs were treated with pdFIX anymore. Compared to the period before 2016, the inhibitor incidence in SHA-PUPs as assessed in EUHASS was significantly reduced from 24% to 6%, and a potential reduction from 9% to 3% ($p = 0.066$) was observed in SHB-PUPs. Inhibitor development in PTPs remained stable around 0.9/1000 treatment years for SHA-PTPs and 0.3/1000 treatment years for SHB-PTPs.

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TABLE 1 | Treatment and inhibitor development in severe haemophilia according to period, exposure status and diagnosis.

	2008–2015		2016–2022		
SHA PUP (number)	**743 (total)**	**In 2015**	**831 (total)**	**In 2022**	***p* value**
on pdFVIII	13%	12%	18%	17%	
on SHL-rFVIII	87%	87%	56%	21%	
on EHL-rFVIII	0%	1%	13%	17%	
on emicizumab	0%	0%	13%	44%	
FVIII inhibitors (n)	182		131		
FVIII inhibitor (cumulative incidence)	24%		16%		<0.0001
SHB-PUP (number)	**115 (total)**		**121 (total)**		
on pdFIX	26%	10%	17%	0%	
on SHL-rFIX	74%	90%	29%	21%	
on EHL-rFIX	0%	0%	54%	79%	
FIX inhibitors (n)	10		4		
FIX inhibitor (cumulative incidence)	9%		3%		0.066
SHA PTP (treatment years)	**36,270 (total)**		**38,242 (total)**		
on pdFVIII	29%	27%	21%	15%	
on SHL-rFVIII	71%	78%	50%	28%	
on EHL-rFVIII	0%	0%	19%	32%	
on emicizumab	0%	%	9%	26%	
FVIII inhibitors (n)	38		28		
FVIII inhibitor rate/1000 years	1.05		0.73		0.151
SHB PTP (treatment years)	**5797 (total)**		**6262 (total)**		
on pdFIX	38%	34%	20%	15%	
on SHL-rFIX	62%	66%	35%	15%	
on EHL-rFIX	0%	0%	44%	70%	
FIX inhibitors (n)	1		3		
FIX inhibitor rate/1000 years	0.17		0.48		0.415

5.1 | Strengths and Limitations

We believe that these data are representative for Europe since EUHASS has representation from the majority of European countries and includes a wide variety of treatment strategies and CFCs [19–21]. Moreover, the number of PUPs and treatment years in PTPs have remained quite stable over the years, as well as the inhibitor rates observed until the introduction of the new treatment modalities around 2016. Due to the anonymous data collection, the data for the noninhibitor patients are collected only at group level: annually for PTPs and at reaching 50 EDs for the PUPs. This results in delayed detection of changes in inhibitor rates [17], and data checking can only be performed at group level by logical checks. However, inhibitor rates have always been in accordance with those from other registries, especially for PUPs, which are most often reported [22–24]. Emicizumab in SHA-PUPs poses a challenge for the detection of inhibitors according to the FVIII concentrates: these PUPs on emicizumab prophylaxis still occasionally receive CFCs, leading to a significant delay in reaching 50 EDs, which could be postponed for 5–10 years or more. Moreover, the EUHASS datacollection system was not designed to include treatment with more than one medication, except for bypassing agents. Consequently, especially for PUPs without inhibitors data-registrars may have entered data on PUPs completing 50 EDs on emicizumab or reported at the time of completing 50 EDs on FVIII only, while disregarding EDs on emicizumab. The data indicate that registrars have counted the exposures on emicizumab, rather than on FVIII, which are postponed by use of emicizumab. Counting the FVIII exposures would result in a lower number of SHA-PUPs reported per

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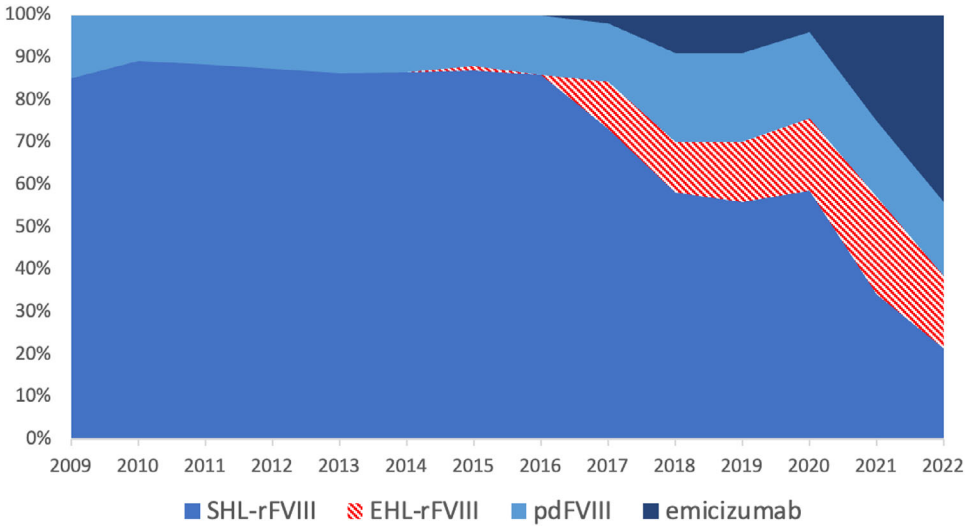

FIGURE 1 | Treatment in PUPs with severe haemophilia A over time.

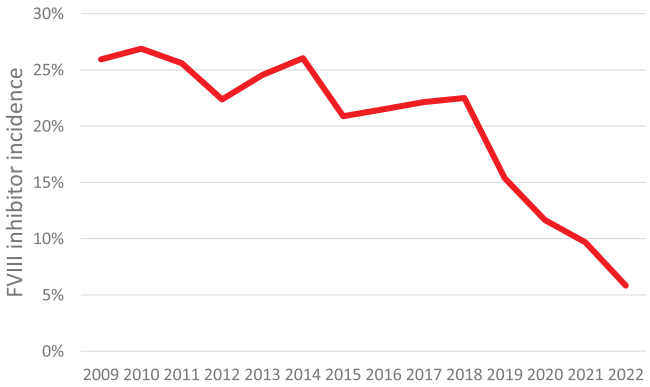

FIGURE 2 | Inhibitor development in PUPs with severe haemophilia A over time. The FVIII inhibitor incidence in SHA PUPs assessed by EUHASS showed a steep decline over the last 6 years. This may be caused by delayed exposure to FVIII during prophylaxis with nonreplacement therapy and/or EHL-FVIII, and subsequent delayed detection of inhibitors. Therefore, these data may present and underestimation of the true FVIII inhibitor incidence in SHA PUPs.

year, but this was not observed. Overall, it is expected that the present data included an underestimation of the true incidence of FVIII-inhibitors.

5.2 | Clinical Implications

The observation that more than 95% of the inhibitors in PUPs occur in the first 50 EDs, stems from the days of early prophylaxis with CFCs [23, 25]. The lower intensity of exposure, especially to FVIII in the era of emicizumab, but also to FIX due to prophylaxis with lower frequencies with EHL-rFIX, may modify the immunological mechanisms of inhibitor development. Nonreplacement therapies will likely be introduced in SHB-PUPs too, and the less intensive treatment regimens could postpone inhibitor detection for PUPs with both SHA and SHB. Indeed, inhibitor development in SHA-PUPs receiving only FVIII concentrates showed a steep and statistically significant decline (Figure 1), which could not be explained by a reduced inhibitor risk associated with EHL-rFVIII concentrates. These developments will render the inhibitor risk assessment for the novel and recently introduced FVIII concentrates even more challenging. It is unclear whether inhibitor risk has truly changed for young boys exposed to FVIII concentrates or whether it will be delayed and will eventually develop when patients are treated with FVIII in at least 50 EDs over the years.

The data on a potential reduction of inhibitor development for SHB-PUPs is difficult to interpret. Inhibitor development may truly show a reduction, but this could not be explained by a reduced inhibitor development on EHL-rFIX only. As indicated by the overlapping confidence intervals, this 'reduction' may still be a chance finding.

5.3 | Future Studies

The choice of any CFC depends on efficacy and side effects, especially inhibitor development, and continuous monitoring of inhibitor development remains mandatory. As the method of data collection of the denominator of the inhibitor development for PUPs in EUHASS depends on reporting the number of PUPs completing 50 EDs per CFC, this will be delayed and difficult to register for the centres. Therefore, it was decided to abandon this data collection from 2023 onwards. Consequently, monitoring of inhibitor development will have to continue in other (inter)national registries and can only be done by the collection of details of the exposure to both nonreplacement therapy and CFC. This effort requires detailed data collection and informed consent at patient level, as is obtained in most national registries [26–28].

In conclusion, EUHASS showed progressive uptake of new treatments since 2015. A large proportion of SHA switched to emicizumab, and this coincided with a steep reduction in the number of inhibitors reported in SHA-PUPs. However, this downward trend in inhibitor incidence may be caused by delayed exposure to FVIII and, therefore, represents a temporary phenomenon. For SHB, vast majority of PUPs and PTPs had switched to EHL-rFIX,

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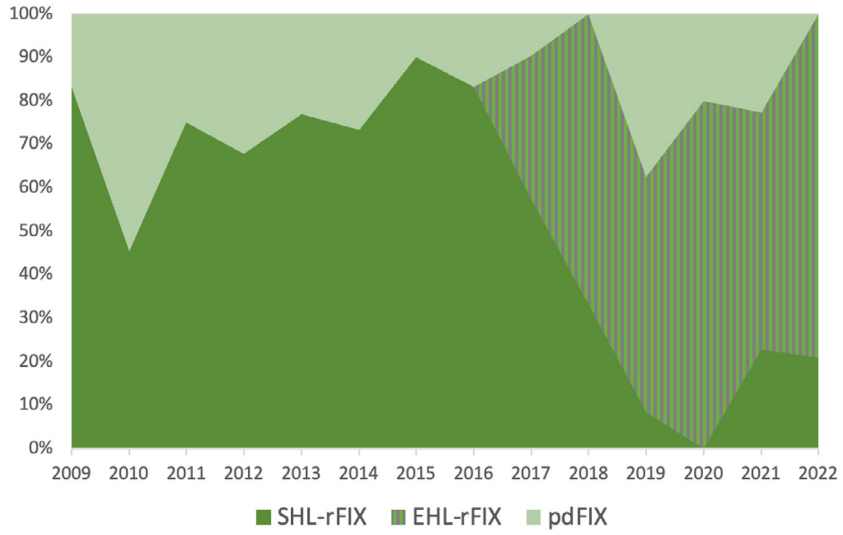

FIGURE 3 | Treatment in PUPs with severe haemophilia B over time.

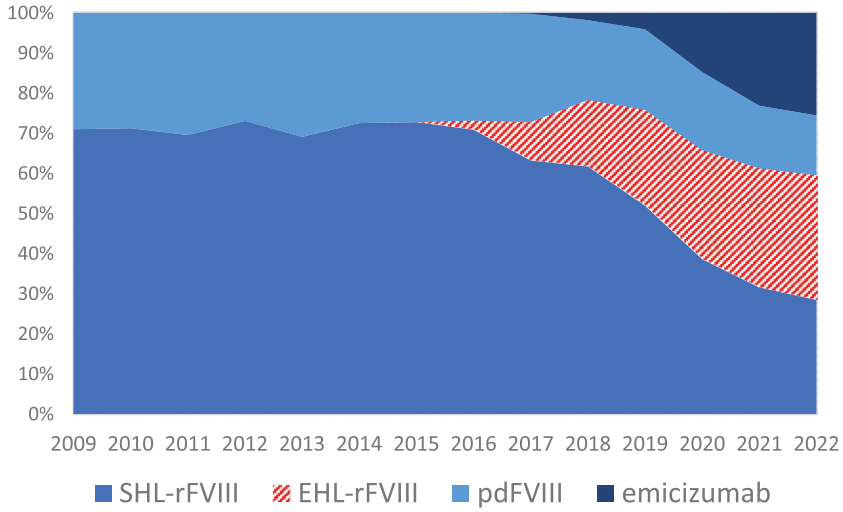

FIGURE 4 | Treatment in PTPs with severe haemophilia A over time.

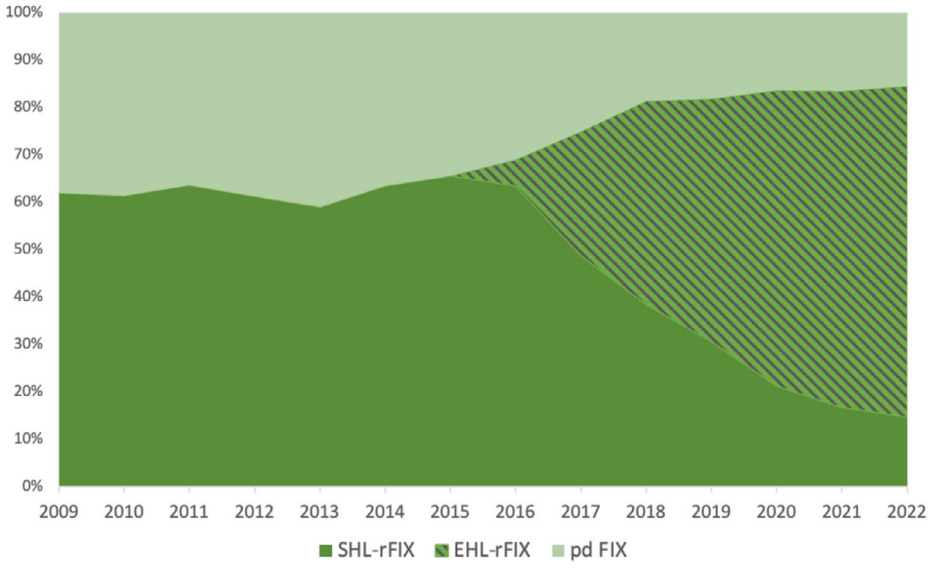

FIGURE 5 | Treatment in PTPs with severe haemophilia B over time.

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and a potential trend towards lower inhibitor development in SHB-PUPs was observed.

Although the full impact of new treatments on inhibitor development still needs to be established, it is evident that monitoring of the inhibitor development for novel and recently introduced CFCs will be more difficult but continues to be important.

Author Contributions

All authors conceived and designed the study. Michael Makris, Diana Carbonero, Rob Hollingsworth and Kathelijn Fischer coordinated and performed data checking. Kathelijn Fischer planned and undertook the statistical analyses. All authors performed data interpretation. Kathelijn Fischer drafted the manuscript, which was completed with input from all authors. All the authors approved the final manuscript. Data collection was performed by Diana Carbonero, Kathelijn Fischer, Riitta Lassila, Flora Peyvandi, Alex Gatt, Thierry Lambert, Samantha C. Gouw, Michael Makris and all centres collaborating in the EUHASS registry. Lists of collaborators to the EUHASS registry are provided in the Supplementary Material.

Ethics Statement

Prior to study entry, all centres approached their institutional review board for approval, which was obtained, if required.

Conflicts of Interest

K.F. has acted as a consultant and participated in expert groups for Bayer, Biogen, CSL Behring, NovoNordisk, and SOBI, has received research grants from Bayer, NovoNordisk, Pfizer, and has given invited educational lectures for Bayer, NovoNordisk, and Pfizer, and has received travel support from Sobi and Bayer. R.L. received honoraria for advisory board participation for CSL Behring, NovoNordisk, Pfizer, Sanquin and Sobi. F.P. participated in the advisory board of CSL Behring, Biomarin, Roche, Sobi, Sanofi and has given invited educational lectures and symposia for Takeda and Spark. A.G. reported no competing interests. R.H. is CEO at MDSAS. T.L. received honoraria for consultancy, advisory board participation and/or invited educational lectures from Baxter, Bayer, CSL Behring, and Pfizer. R.K. received research funding from Bayer and consulting or lecture fees from Bayer, BioMarin and Pfizer. S.G. received an unrestricted medical research grant from Sobi D.C. reported no competing interests M.M. has received honoraria for lecturing and grant reviewing from NovoNordisk, Takeda, Grifols and Sanofi.

Data Availability Statement

Data will be made available upon request, conditional on approval of the EUHASS Steering Committee.

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