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ORIGINAL ARTICLE

Inhibitor development upon switching from plasma-derived to recombinant factor VIII in previously untreated patients with severe hemophilia A: the PUP-SWITCH study

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Abstract

Background: The SIPPET randomized clinical trial showed that in previously untreated patients (PUPs) with severe hemophilia A, treatment with plasma-derived factor (F)VIII (pdFVIII) within the first 50 exposure days (EDs) was associated with a lower

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cumulative incidence of inhibitors than with recombinant FVIII (rFVIII). Switching to rFVIII beyond 50 EDs with pdFVIII is a treatment often implemented by many centers. The question is whether or not this switch may induce a risk of inhibitor development.

Objectives: We investigated if in PUPs with severe hemophilia A switched after 50 EDs from pdFVIII to rFVIII, a novel inhibitor peak appears.

Methods: The PUP-SWITCH observational retrospective study was designed to investigate the cumulative incidence of novel inhibitors after switching PUPs to rFVIII after 50 and before 150 EDs. Hemophilia centers that routinely switched PUPs from pdFVIII to rFVIII within this exposure time frame were invited to participate. Patients were followed up for at least 50 EDs after the switch.

Results: Ninety-seven patients were evaluated, and 87 were included according to eligibility criteria between 2020 and 2022. Only one of them developed an inhibitor 20 EDs after switching, so the cumulative incidence was 1.15% (95% CI, 0.03%-6.24%).

Conclusion: PUP-SWITCH, a study focusing on PUPs undergoing a product class switch from pdFVIII to rFVIII after 50 EDs, showed that switching appears to be safe pertaining to the risk of development of new inhibitors.

KEYWORDS
factor VIII, factor VIII/adverse events, factor VIII/immunology, factor VIII/therapeutic use, hemophilia A/drug therapy

Essentials

- Plasma-derived factor (F)VIII causes fewer inhibitors in previously untreated patients with severe hemophilia A.
- PUP-SWITCH investigated the inhibitor risk of switching from plasma-derived to recombinant FVIII.
- One of 87 patients developed an inhibitor after switching (cumulative incidence, 1.15%).
- Switching from plasma-derived to recombinant FVIII after 50 exposure days appears to be safe.

1 | INTRODUCTION

Several observational studies and systematic reviews suggested a higher risk of inhibitor onset with recombinant factor (F)VIII (rFVIII) than plasma-derived FVIII (pdFVIII) in previously untreated patients (PUPs) with severe hemophilia A during the critical phase of the first 50 exposure days (EDs) to FVIII [1–5]. SIPPET, the first randomized controlled trial that tackled this issue in 251 PUPs, showed that during the first 50 EDs, the cumulative incidence of inhibitors was 27% with pdFVIII and 45% with rFVIII [6]. The European Haemophilia Safety Surveillance System (EUHASS) prospective European register and the CHESS Canadian register confirmed the SIPPET findings in 1392 PUPs in a real-world context by combining 8 to 11 years of data from Europe and Canada [7]. Numerous observational studies have shown that patients treated with FVIII for at least 150 EDs, referred to as previously treated patients (PTPs), have a low risk of inhibitor development, approximately 100 times lower than in PUPs [8–10]. For instance, PedNet, the largest prospective cohort study on hemophilia births since the year 2000, investigated the risk of inhibitor development in PUPs with severe hemophilia A until 1000 EDs, showing that in more than 1000 PUPs, the cumulative inhibitor incidence was 28.9% at 50 EDs and 29.9% at 75 EDs, the latter representing a near-0 risk plateau of inhibitor development (Supplementary Table S1) [11]. Because a change of FVIII product implies exposure to new antigens after the achievement of tolerization [12], product switching led to early concerns of neo-immunogenicity at the time of inhibitor outbreaks in Belgium and The Netherlands because switching PTPs to 2 different pdFVIII products was associated with an up to 5-fold inhibitor increase, ie, 20 per 1000 patient-years [13–15]. The Dutch and Belgian PTP cases had been newly treated with pdFVIII products that underwent viral inactivation processes based upon long-duration pasteurization, which caused structural changes to FVIII and unexpected neo-immunogenicity [16,17]. Hence, doubts remain on whether switching among products of the same or different classes is associated with a clinically relevant inhibitor increase. This question is more relevant now with the availability of several new FVIII products, ie, whether or not patients with severe hemophilia A can switch to another product before being exposed to FVIII for 150 EDs. A treatment strategy based upon the use of pdFVIII in the early high-risk period of 50 EDs followed by a switch to rFVIII would combine

the benefits of both classes of products, ie, lower inhibitor risk in the early phase with pdFVIII and the potential reduction by 20% to 30% of the number of the yearly intravenous infusion in patients employing rFVIII with extended plasma half-life [12]. With this background, a therapeutic strategy of 50 initial EDs with pdFVIII followed by a switch to rFVIII (standard or extended half-life) may become a choice for many hemophilia centers, provided the incidence of inhibitors after switching is no higher than that observed in PTPs. Indeed, many patients worldwide have been treated according to this strategy after the SIPPET results [12,17], but the outcome data have not been routinely collected [18]. Given this gap of knowledge, we designed the PUP-SWITCH retrospective observational study with the goal to make use of the data obtained in patients treated in the real world with the aforementioned switching strategy that would combine the benefits of both classes of products [19].

2 | METHODS

2.1 | Study design

PUP-SWITCH is an international, multicenter, retrospective observational cohort study on inhibitor occurrence in PUPs/minimally treated patients (MTPs) with severe hemophilia A aged 6 years or less at the time of initiating FVIII replacement therapy. MTPs were defined as those treated no more than 4 times with blood components. Patients treated with a pdFVIII prophylactic regimen initiated within the 10th ED and who did not develop an inhibitor during the early high-risk treatment phase (first 50 EDs) were subsequently switched to a single rFVIII product in the window of 50 to 150 EDs. Cases had to attain the switch inhibitor-free and have a follow-up of at least 50 EDs or 2 years of treatment after switching (Supplementary Figure S1). Exclusion criteria were developing an inhibitor prior to switching, switching outside the window of 50 to 150 EDs, and changing to multiple products during the postswitch follow-up. Per protocol, patients treated with a pdFVIII prophylactic regimen who started prophylaxis within the 10th ED were eligible. The project received ethical approval from the Coordinating Center Milan Area 2 Committee and from those of the other participating centers (not needed only for Turkish centers).

2.2 | Study outcomes

The primary endpoint was the cumulative incidence of inhibitors after switching from pdFVIII to any rFVIII product. Secondary endpoints were the pattern of inhibitor development, the number of EDs at incidence, titer at onset, peak titer, persistence/transience of the inhibitor, risk factors such as age at first treatment, family history of hemophilia and inhibitor, and the *F8* gene mutation type. Null mutations were defined as the intron 22 inversion, large deletions/duplications, nonsense and frameshift mutations; non-null mutations were missense, splice site, polymorphisms only, and no identified mutation.

2.3 | Sample size calculation

In 2015, the International Society on Thrombosis and Haemostasis (ISTH) Subcommittee on Factor VIII, Factor IX and Rare Coagulation Disorders provided recommendations on the design of clinical studies for the evaluation of the risk of new inhibitor onset in PTPs with severe hemophilia A [18]. Accordingly, immunological scenarios on neo-immunogenicity in the different ED phases of FVIII exposure were chosen to provide an estimate of the sample size needed to evaluate the incidence of new inhibitors. By prefixing a maximum tolerable risk, the studies were sized to rule out a greater than acceptable risk of FVIII product neo-immunogenicity in PTPs [20]. Two main phases for the inhibitor risk were defined as suggested by Rosendaal et al. [14] in 1993:

- Phase 1—epidemic phase (0-50 EDs): inhibitor incidence of 30%, the measured outcome being cumulative incidence (events/people) [14,21].
- Phase 2—endemic phase (50-150 EDs): inhibitor incidence rate of 4/100 person-years, the measured outcome being the exclusion of a higher than acceptable incidence (/person-years) [14].

In phase 2, the sample size depends on both the predefined rate of inhibitor development to be excluded and the person-time accrued in the study. One or fewer than one inhibitor event in 80 subjects is required to rule out a 6.8% cumulative incidence of new inhibitors after 50 EDs based on the upper level of the 95% CI in a Poisson distribution [21]. Accordingly, by setting the non-inferiority margin (rule-out risk) at 7%, assuming 1% inhibitor incidence, and expecting a non-evaluable case rate of 10%, a sample size of 88 cases was calculated, with a total of 80 eligible patients needed to obtain 80% power.

2.4 | Data collection and management

A global questionnaire was administered from January to March 2018 to 1325 hemophilia treatment centers (HTCs) listed in the directory of the World Federation of Hemophilia and the hemophilia central website developed within the European Haemophilia Network project. Emails were effectively delivered to 1010 HTCs. Of them, 126 filled out the questionnaire [12], and 56 initially expressed interest in participating in this study, but only 20 had performed the switch according to local practice and the PUP-SWITCH standards and ultimately chose to participate. These 20 centers (Supplementary Text S1) submitted surveys, but only 15 of them had patients who met all inclusion/exclusion criteria. The PUP-SWITCH data collection survey was designed on the ISTH REDCap platform (Vanderbilt University) and accessible on the ISTH website to create further visibility and invite HTCs to participate in the study [22]. Following informed consent, demographic data, clinical profiles, laboratory data, and therapeutic regimens were extracted from clinical charts and inserted into the protected electronic database.

2.5 | Laboratory methods

All participating centers used the Bethesda assay, with or without Nijmegen modification, to detect and measure the inhibitor [23]. The frequency of testing was at the discretion of each center, depending on the frequency of replacement with rFVIII and per local practice. Positivity cutoff varied from 0.4 to 0.6 BU in different centers.

2.6 | Statistical analysis

For nonnormally distributed parameters, medians and IQRs were reported. Incidence rates and cumulative incidences were calculated by person-years and time-to-event survival methods, with error margins based on Poisson and binomial distributions. Incidence rates were calculated as the number of new inhibitors divided by total follow-up time in years and EDs, multiplied by 1000 to obtain an incidence rate in cases per 1000 person-years or person-EDs. The R software (R Core Team) was used for statistical analysis.

3 | RESULTS

3.1 | Study population characteristics

A total of 97 surveys were submitted to the PUP-SWITCH platform from 2020 to 2022, of which 87 were eligible and 10 were excluded owing to various noneligibility reasons. Ten centers from Turkey, 3 from Iran, 1 from Germany, and 1 from Egypt ultimately chose to participate (Figure). Baseline characteristics, ethnic origins, treatment characteristics, rFVIII products used, switching features, and follow-up times are shown in Table 1, together with baseline treatment characteristics and switching-related parameters.

Regarding baseline characteristics, the prevalence of null gene mutations was 77%, and that of nonnull mutations was 23% (Supplementary Figure S2). Thirty-nine percent of patients had a positive family history of hemophilia and 12% also of inhibitors (Table 1). Roughly a quarter of patients were from each of the 4 ethnic backgrounds, ie, 29% Iranian, 26% Egyptian, 25% Turkish, and 20% West European (German; Table 1). As per early treatment characteristics, 72% were PUPs and 28% MTPs. The reason for the first treatment was bleeding (58%), prophylaxis (33%), and minor surgery, mainly circumcision (9%). The median age at first treatment was 10 months (IQR, 7-14; Table 1). Patients were switched to rFVIII at a median time of 60 EDs (IQR, 51-73) and had been exposed since then to a median number of 200 EDs (IQR, 108-408), corresponding to a median follow-up of 1.3 years (IQR, 0.97-4.19). The rFVIII products used after switching were all of standard plasma half-life: Xyntha (Pfizer) was the most commonly used (32%), followed by NovoEight (NovoNordisk) (19%), Nuwiq (Octapharma) (17%), SaFacto (Saman Daroo) (14%), ReFacto (Pfizer) (10%), Advate (Takeda) (5%), Kogenate (Bayer) (2%), and Kovaltry (Bayer) (1%; Supplementary Figure S3). SaFacto, the only rFVIII available in Iran due to sanctions [24,25], is a B-domain-deleted FVIII made from a Chinese hamster ovary cell line that, when compared with Xyntha in a randomized trial, showed similar efficacy and safety [26,27].

3.2 | Inhibitor incidence

Frequency of testing after 50 EDs varied from center to center but was on average every 3 to 6 months. The only case who developed an inhibitor was a 2-month-old boy who switched to NovoEight at ED 50 and developed the inhibitor at ED 70. The inhibitor had a low titer (3 BU) at onset, reached a peak (8 BU) at 4 weeks, and was undetectable at 6 weeks. The patient continued treatment with the same rFVIII according to a scheme of low-dose immune tolerance induction for 42 days, changing from 25 IU/kg 3 times weekly before inhibitor detection to 50 IU/kg daily from inhibitor detection until negativity. Only a single dose of factor eight inhibitor bypass activity was administered for the management of a bleeding episode 4 weeks after inhibitor onset. After the inhibitor became undetectable, he returned to prophylaxis at 25 IU/kg twice/wk with the same rFVIII product, and the inhibitor remained negative. Regarding baseline characteristics (Table 1), he had a null *F8* mutation (a large deletion) and a family history of inhibitors. He was an MTP who had historically received 3 infusions of cryoprecipitate to treat a traumatic bleeding event prior to initiation of FVIII replacement with Koate (Kedrion) at the age of 2 months.

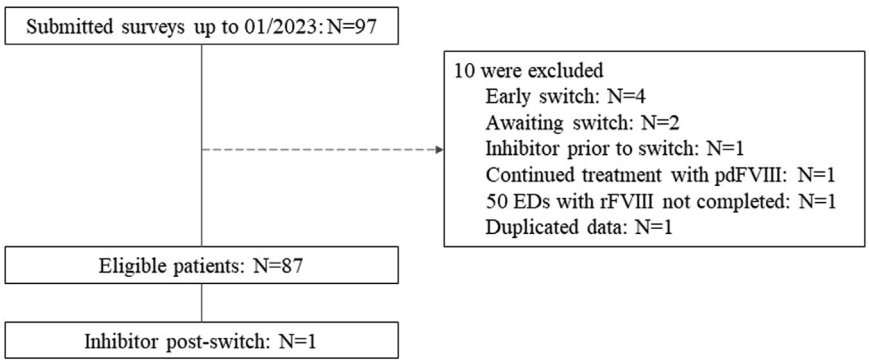

FIGURE Study flowchart. ED, exposure day; pdFVIII, plasma-derived factor VIII; rFVIII, recombinant factor VIII.

TABLE 1 Patient population characteristics.

Characteristics	All (*n* = 87)	Inhibitor (*n* = 1)
Baseline		
Type of *F8* mutation, *n* (%)		
Null	44/57 (77)	1
Non-null	13/57 (23)	
NA	30/87 (35)	
Family history of hemophilia, *n* (%)		
No	53/87 (61)	
Yes	34/87 (39)	1
Family history of inhibitor,[a] *n* (%)		
No	30/34 (88)	
Yes	4/34 (12)	1
Country, *n* (%)		
Turkey	22/87 (25)	
Iran	25/87 (29)	
Germany	17/87 (20)	
Egypt	23/87 (26)	1
Treatment		
Previous treatment, *n* (%)		
PUP	62/87 (71)	
MTP	25/87 (29)	1
Age at first FVIII infusion (mo)	10 (7-14)	2
Reason for first treatment, *n* (%)		
Prophylaxis	28/87 (32)	
Bleeding	51/87 (59)	1
Surgery	8/87 (9)	
Switch		
ED of switch	60 (51-73)	50
EDs with rFVIII after switch	200 (108-408)	20
Total EDs before and after switch	270 (176-505)	70
Years of follow-up after switch	1.33 (0.97-4.19)[b]	0.15

Continuous variables are expressed as medians (IQR: P25-P75).

ED, exposure day; MTP, minimally treated person; NA, not available; Null, nonnull; PUP, previously untreated person; rFVIII, recombinant factor VIII.

[a]Data reported on the 34 patients with a positive family history of hemophilia.

[b]Data available from 84 patients.

Years at risk were calculated according to 2 different time measures, ie, EDs and years (Table 2). The total time at risk for the whole PUP-SWITCH cohort was 4320 EDs (data on 87 patients), corresponding to 224.15 years (data on 84 patients). Incidence rates with person-EDs and person-years, as well as the cumulative incidence, are in Table 2. Taking calendar dates corresponding to this follow-up time, the incidence rate was 4.46 per 1000 person-years (95% CI, 0.63-31.53). The cumulative incidence of inhibitor development after switching was 1.15% (95% CI, 0.03%-6.24%).

4 | DISCUSSION

In this study, the incidence of novel inhibitors was evaluated after switching PUPs from the product class known to be less immunogenic (pdFVIII) to a potentially more immunogenic one (rFVIII) as soon as the early, more vulnerable phase had elapsed (50 EDs). The present PUP-SWITCH study found a small risk of inhibitor development upon switching: only 1 of 87 developed an inhibitor. This patient was at high risk owing to a positive family history of inhibitor as well as for a high-risk deletion mutation. The cumulative inhibitor incidence was 1.15% (95% CI, 0.03%-6.24%), and the rate of inhibitor incidence was 4.46 in 1000 person-years (95% CI, 0.63-31.53). The upper limit of the cumulative incidence was smaller than the noninferiority margin of 7% priorly stipulated to rule out an unacceptably high inhibitor risk after switching. This low incidence is roughly in line with the results from national and international postmarketing surveillance registries, preregistration trials, and meta-analyses on PTPs that overall reported an incidence of about 2 per 1000 patient-years but with a high degree of variability [1,8,28–31]. Before our study, data on this issue were provided by the CANAL and PedNet-Rodin cohorts (in 104 and 20 PUPs, respectively) [32], as well as by studies carried out in mixed populations of PUPs and PTPs from Italy [33], the United Kingdom [34], and Ireland [35]. On the whole, these earlier studies documented a low inhibitor incidence in switched cases. However, the studies were not specifically designed to evaluate the safety of switching, dealt with heterogeneous populations of PUPs and PTPs with different background inhibitor risks, and were based on switching that occurred at varied time points. In addition, a Delphi consensus was on the whole favorable to switching from pdFVIII to rFVIII, but with some concerns and caveats (switching prior to 50 EDs, immediately prior to surgery or intensive treatment, in patients with a past history of inhibitors, and those treated on-demand) [36]. The 2018 meta-analysis that found a rate of 2.06 per 1000 person-years (95% CI, 1.06-4.01) also included cases with moderate hemophilia A [28]. Very recently, the EUHASS register reported an inhibitor rate of 1 per 1000 treatment years (95% CI, 0.80-1.30) in PTPs with severe hemophilia A after 50 EDs followed up until 1000 EDs of treatment with pdFVIII and rFVIII of standard or extended half-life [37]. Kempton et al. [29] reported an incidence rate of 2.14 in 1000 person-years in their observational cohort study of patients treated with both pdFVIII and rFVIII. The McMillan 1988 report, taken as a yardstick reference of inhibitor rate in PTPs, reported a rate of 8 per 1000 person-years [30]. This generally low incidence of inhibitors makes it difficult to perform association analyses to establish the potential risk factors underlying inhibitor development in PUPs turning to PTPs.

TABLE 2 Inhibitor incidence rates using different time measures and cumulative incidence.

EDs	End of observation = 50 EDs	End of observation = years accrued at 50 EDs
N	87	84
Time measure	EDs	Years
Time at risk	4320	224.15
Incidence rate	23.15 per 1000 person-100 EDs	4.46 per 1000 person-years
Incidence rate 95% CI	1.26-164.29	0.63-31.53
Cumulative incidence	1.15%	
Cumulative incidence 95% CI	0.03-6.24	

Person 100-EDs is defined as number of patients followed up for 100 EDs.
ED, exposure day.

Among the limitations of this study, we recognize potential misclassification bias (eg, missing inhibitor detection due to heterogeneous testing frequency, different assays, and positivity cutoffs), as well as the variability of products and therapeutic regimens adopted by participating centers. All the hemophilia centers chose to switch to standard half-life recombinant products, and no case was switched to an extended half-life recombinant product. Standard half-life rFVIII is still largely used in the real world, but it would be of interest to see whether the same low inhibitor risk after switching applies to extended half-life rFVIII products. Nonetheless, to date, PUP-SWITCH is the only study specifically designed to evaluate the safety of a product class switch in PUPs with severe hemophilia A transitioning to PTPs.

In conclusion, PUP-SWITCH showed that after 50 EDs, a switch from pdFVIII to rFVIII in PUPs with severe hemophilia A appears to be safe pertaining to the risk of development of new inhibitors.

APPENDICES

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AUTHOR CONTRIBUTIONS

F.R.R. conceptualized the study. F.P. and S.M. coordinated and carried out the study in all aspects in quality of representatives of the PUP-SWITCH Study Group. S.M. collected and analyzed the data and wrote the manuscript. Other coauthors were involved in either patient evaluation, inclusion, and data insertion or in the data monitoring process. P.M.M. and F.P. critically revised the manuscript. All authors read and approved the final paper.

RELATIONSHIP DISCLOSURE

F.P. has participated in educational meetings and the advisory board of Sanofi, Sobi, Takeda/Spark, Roche, BioMarin, and CSL Behring. P.M.M. has received Roche, Takeda, and Werfen honoraria for lectures at educational symposia. G.N. has received speaker fees from Roche and Pfizer. The rest of the authors did not report any competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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