A Retrospective Observational Study of Rurioctocog Alfa Pegol in Clinical Practice in the United States

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ABSTRACT

BACKGROUND: Research describing patient experience and outcomes with extended half-life recombinant factor VIII (EHL rFVIII) outside of clinical trials is limited. Real-world rFVIII consumption studies, when people with hemophilia A (PWH) switch from standard half-life (SHL) to EHL rFVIII, may help payers and clinicians make more informed treatment choices.

OBJECTIVE: To conduct a retrospective, observational, U.S.-based analysis to describe clinical and demographic profiles of PWH who switched to prophylactic rurioctocog alfa pegol.

METHODS: Data were obtained from PWH treated by 38 prescribers across 21 states using specialty pharmacy database case report forms, electronic medical records, and direct communication with providers, PWH, or their guardians. Assessments included disease severity, pain severity, number and location of target joints, prior HA therapy, reasons for switching, treatment duration, dosing frequency, adherence, and annualized bleeding rates (ABRs) before and after switching to rurioctocog alfa pegol from SHL or another EHL rFVIII.

RESULTS: Data were collected from 56 PWH. The mean age was 26 years (range = 5–88); median age was 24 years (interquartile range = 14–34); 20% were aged < 12 years; and 89% (50/56) had severe HA. All PWH had ≥ 12 months of rFVIII treatment before switching to rurioctocog alfa pegol. The population had a mean 1.8 target joints. Baseline subjective pain assessment was mild to moderate for 68% (38/56) of respondents. Before receiving rurioctocog alfa pegol, most PWH received antihemophilic factor (recombinant) for prophylaxis (73%, 41/56) or breakthrough bleeding (59%, 33/56). Mean dosing frequency for prior prophylaxis was 2.8 per week for SHL rFVIII and 1.8 per week for EHL rFVIII, and 2.2 per week for all PWH after switching to rurioctocog alfa pegol prophylaxis. The median time on rurioctocog alfa pegol prophylaxis was 12.0 months versus 80.8 months on previous SHL rFVIII and 13.5 months on previous EHL rFVIII. Mean ABRs on prior prophylaxis were 5.9 for SHL rFVIII (n = 35) and 4.7 for EHL rFVIII (n = 3). After switching to rurioctocog alfa pegol, the overall mean ABR reduced by 71% (5.8 to 1.7, $P < 0.001$) and 20/56 PWH had no bleeding events. There was also a 20.9% reduction in the mean days per week of factor administration ($P < 0.001$) after switching to prophylactic rurioctocog alfa pegol. For 47 PWH who switched from SHL rFVIII, their weekly dose decreased from 109.8 to 100.6 IU per kg with rurioctocog alfa pegol ($P = 0.094$). The proportion of PWH with good/complete treatment adherence increased from 68% (38/56) on any prior rFVIII to 80% (45/56) on rurioctocog alfa pegol. The most common reason PWH switched to rurioctocog alfa pegol was to reduce treatment infusions.

CONCLUSIONS: Switching from either an SHL or EHL rFVIII to rurioctocog alfa pegol is associated with fewer bleeding episodes owing to more effective prophylaxis and improved adherence. Those who switched from an SHL rFVIII reported reduced factor consumption with rurioctocog alfa pegol. This long-acting factor is an important additional option for the care of PWH.

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What is already known about this subject

- The need for regular infusions with standard half-life recombinant factor VIII (SHL rFVIII) may have a high treatment burden on people with hemophilia A (PWH) and their caregivers.
- There is a paucity of research describing the patient experience and outcomes with extended half-life (EHL) rFVIII outside of clinical trials.
- Real-world rFVIII consumption studies, when PWH switch from SHL FVIII to rurioctocog alfa pegol, may assist with treatment decisions.

What this study adds

- This is the largest study, outside of a clinical trial setting, that has assessed clinical profiles and rFVIII consumption among PWH who switched to rurioctocog alfa pegol from an SHL or other EHL rFVIII therapy.
- These real-world data indicate that switching from an SHL rFVIII to rurioctocog alfa pegol is associated with fewer bleeding episodes owing to more effective prophylaxis, and with reduced factor consumption and increased adherence.
- This long-acting factor is an important additional option for the care of PWH.

Hemophilia A (HA) is an X-linked congenital bleeding disorder caused by deficient or defective coagulation factor VIII (FVIII).¹ The predominant clinical characteristic of HA is repeated bleeding episodes, which cause acute or long-term threats to health including chronic joint disease. These effects reduce the patient's health-related quality of life.²

As the primary aim of HA management is to prevent bleeding episodes, the current standard of HA care is prophylactic replacement treatment with recombinant FVIII (rFVIII) concentrates.^{3,4} The half-lives of standard half-life (SHL) rFVIII products are ~10–14 hours, requiring intravenous infusion every other day or 3 days per week.^{5,6} Patient survey data suggest that the time-consuming nature of prophylactic FVIII regimens is the most important barrier to treatment adherence in HA care.^{7,8}

In 2014, the first-generation extended half-life (EHL) rFVIII, Fc fusion protein (rFVIII-Fc), received U.S. Food and Drug Administration approval for the treatment of HA.^{9–11} With EHL rFVIII products becoming available for

people with hemophilia A (PWA), fewer treatment infusions are needed (~2 infusions per week), so the burden of prophylactic rFVIII administration is reduced.⁷ There is no uniform definition of an EHL rFVIII product, although an evidence-based review has proposed the defining characteristics to help clinicians and patients select the most appropriate rFVIII product.¹²

Rurioctocog alfa pegol (Adynovate [U.S.]/Adynovi [Europe]; Baxalta U.S. Inc., a Takeda company, Lexington, MA) is a novel third-generation EHL rFVIII based on antihemophilic factor (recombinant) (Advate; Baxalta U.S. Inc., a Takeda company, Lexington, MA), with a modified polyethylene glycol A component.¹³⁻¹⁵ This modification increases the half-life of the rFVIII by 1.4 to 1.5-fold compared with SHL rFVIII.^{5,16} Since the introduction of first-generation EHL rFVIII, there has been an increase in clinical data supporting the use of EHL rFVIII for FVIII replacement treatment in PWA.¹² However, publications of real-world outcomes data with EHL rFVIII such as rurioctocog alfa pegol are limited,³ because of the relatively recent approval by the U.S. Food and Drug Administration and availability of EHL rFVIII products.^{11,13,17,18} This represents a knowledge gap in the current understanding of the effect of EHL rFVIII on disease burden in the clinical practice setting.

A specific concern for payers is that real-world rFVIII consumption, by far the greatest lifetime cost input of HA,⁷ may be different from that observed in clinical studies. This issue is highly pertinent when considering real-world use of EHL rFVIII, because recently published data on the financial cost of switching from an SHL to an EHL rFVIII show that, on average, EHL rFVIII products are more costly per patient per year (cost increase of 67.8%).¹⁹

Compared with SHL rFVIII, the dose of EHL rFVIII is higher per infusion but with a reduced dosing frequency. As a result, although data from clinical trials indicate that overall consumption is similar for SHL and EHL rFVIII products,^{20,21} there could still be concern among payers that the overall consumption of EHL rFVIII may be higher than SHL rFVIII. The clinical characteristics of PWA who switch treatments, their reasons for switching treatments, and their health status as a result of switching to EHL rFVIII should be taken into account when considering overall rFVIII consumption.

This retrospective, observational, U.S.-based analysis was conducted to describe the clinical and demographic profiles of PWA who switched from prophylaxis with any rFVIII product to prophylactic rurioctocog alfa pegol. In addition, the real-world consumption of rurioctocog alfa pegol and its relationship with clinical outcomes and treatment adherence were assessed.

Methods

Data Collection

A convenience sample of 120 specialty U.S. pharmacies were contacted; 17 indicated dispensing data for >1 PWA treated

with rurioctocog alfa pegol, and 3 specialty pharmacies that serviced patients who met the study inclusion criteria were selected for analysis. Data were collected using specialty pharmacy database case report forms, electronic medical records, and standard data collection forms for completion by providers, clinicians, and PWA or their guardians. Enrolled study clinicians and specialty pharmacies signed compliance agreements regarding the disclosure of patient information to the shared prescription database. PWA or their guardians signed electronic informed consent forms designed by the Trio Health Advisory Group (La Jolla, CA).

Patients

Eligible PWA had received previous treatment with a prophylactic rFVIII product for ≥ 12 months before switching to rurioctocog alfa pegol. PWA were only eligible for the study if they had received the approved prophylaxis dosage regimen of rurioctocog alfa pegol during the course of the study, defined as 40-50 IU per kg body weight twice weekly.¹³ Exclusion criteria were the participation in a rurioctocog alfa pegol clinical trial before or during the study period and the presence of FVIII inhibitory antibodies requiring treatment and/or the use of immune tolerance induction during the study period.

Assessments and Endpoints

Baseline patient characteristics collected included disease severity, prior HA therapy, number and location of target joints, level of pain (patients were asked to describe their pain levels on a scale of 1 to 5; 1=mild pain, 5=severe pain), and annualized bleeding rates (ABRs). ABRs for prior therapies were recorded as the number of bleeds in the 12 months before switching to rurioctocog alfa pegol.

Measured endpoints before and after switching to rurioctocog alfa pegol included ABRs, months on therapy, and ordinal treatment adherence based on a subjective assessment by the PWA (from prescriptions filled, 100% is complete adherence, 80%-99% is good adherence, 50%-79% is moderate adherence, and <50% is poor adherence). Factor consumption was measured as the weekly exposure to FVIII (IU per kg). Frequency of treatment administration was assessed as weekly administrations of FVIII. For rurioctocog alfa pegol therapy, the ABR was only calculated if a PWA had received rurioctocog alfa pegol for ≥ 3 months. Excluding patients with <3 months of FVIII prophylaxis is a common approach to evaluating ABR in PWA.²² No safety data were collected for this analysis.

PWA or their caregivers were asked to select their reasons for switching to rurioctocog alfa pegol from a list of 12 options; other user-defined reasons could also be stated. Patients could choose >1 reason.

FIGURE 1 Patient Disposition Flowchart

^aThis analysis assessed the clinical profiles of people with hemophilia A switching from an EHL or SHL rFVIII to rurioctocog alfa pegol and also assessed the real-world consumption of rurioctocog alfa pegol.

^bThis analysis compared the clinical profiles of people with hemophilia A before and after switching from another rFVIII to rurioctocog alfa pegol.

^cFive people with hemophilia A were excluded from the dosing analyses owing to incomplete dosing or frequency information for rFVIII therapy before switching to rurioctocog alfa pegol.

EHL=extended half-life; rFVIII=recombinant factor VIII; SHL=standard half-life.

Statistical Analyses

Continuous variables were assessed using paired 2-tailed t-tests, with $P < 0.05$ regarded as statistically significant. Categorical values were assessed using McNemar's test for case-controlled studies. Analyses were conducted overall and within subgroups stratified by prior prophylactic rFVIII product (SHL or EHL rFVIII) and age group (< 12 years, ≥ 12 years).

Results

Patient Flow and Characteristics

Data were collected from 56 eligible PWA from November 2015 to September 2017 through 3 specialty pharmacies from 38 providers at 32 distinct practices across 21 states (Figure 1). Of the 56 PWA receiving rurioctocog alfa pegol, 2 discontinued treatment before the end of data collection in September 2017 (1 following 3 months of rurioctocog alfa pegol therapy and another following 12 months of therapy). Complete information on dosing and infusion frequency was reported for 51 PWA; this enabled comparison of rFVIII dosing and frequency before and after switching treatment.

The mean age of the study population was 26 years (range=5-88 years); 11 PWA were aged < 12 years and 45 PWA were aged ≥ 12 years (Table 1). Most were Caucasian (63%; 35/56). Overall, the majority of PWA had severe HA

(89%; $n = 50/56$); 1 had mild HA and 5 had moderate HA. The population had a mean 1.8 target joints (median 1); the most common target joint was the ankle (78%; $n = 28/36$). At the time of starting rurioctocog alfa pegol therapy, subjective pain assessments were provided by 41 of 56 PWA, of whom 4% (2/56) indicated severe pain. Of the 46 PWA who provided activity assessments, 63% (29/46) reported being active 7 days per week. PWA predominantly received care from academic hospitals (59%; $n = 33/56$). Insurance coverage was predominantly through commercial payers (46%; $n = 26/56$).

Prior Prophylactic rFVIII Replacement Treatment and Reasons for Switching to Rurioctocog Alfa Pegol

The majority of PWA received SHL rFVIII prophylaxis before switching to rurioctocog alfa pegol prophylaxis (93%; $n = 52/56$), and the remaining 4 patients (7%) received a different EHL rFVIII before switching (Figure 2). Overall, 52 PWA were treated for breakthrough bleeding while on prior SHL or EHL rFVIII prophylaxis; 85% ($n = 44/52$) of these PWA received SHL rFVIII and 4 received EHL rFVIII for prior treatment of breakthrough bleeds. Antihemophilic factor (recombinant) was the most commonly administered rFVIII for prophylaxis and for the treatment of breakthrough bleeding.

TABLE 1 Patient Characteristics

	Prior Prophylactic Therapy Group		Age Group		Total (N = 56)
Variable	Prior SHL (n = 52)	Prior EHL (n = 4)	< 12 Years (n = 11)	≥ 12 Years (n = 45)	
Respondent, n (%)					
Patient/caregiver	19 (37)	1 (25)	3 (27)	17 (38)	20 (36)
Physician	33 (63)	3 (75)	8 (73)	28 (62)	36 (64)
Patient age, years					
Mean (range)	26 (5-88)	25 (17-36)	8 (5-11)	30 (12-88)	26 (5-88)
Median (IQR)	24 (14-34)	24 (19-29)	8 (7-9)	30 (19-35)	24 (14-34)
Patient ethnicity, n (%)					
African American	5 (10)	2 (50)	0 (0)	7 (16)	7 (13)
Caucasian	35 (67)	0 (0)	9 (82)	26 (58)	35 (63)
Latino/Hispanic	4 (8)	0 (0)	2 (18)	2 (4)	4 (7)
Unknown	8 (15)	2 (50)	0 (0)	10 (22)	10 (18)
Geographic spread, n of PWHA (%) ^a					
North Carolina	14 (27)	0 (0)	2 (18)	12 (27)	14 (25)
Ohio	4 (8)	1 (25)	1 (9)	4 (9)	5 (9)
Michigan	4 (8)	0 (0)	1 (9)	3 (7)	4 (7)
Missouri	4 (8)	0 (0)	0 (0)	4 (9)	4 (7)
Other states	26 (50)	3 (75)	7 (64)	22 (49)	29 (52)
Hemophilia severity, n of PWHA (%) ^b					
Mild	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)
Moderate	5 (10)	0 (0)	1 (9)	4 (9)	5 (9)
Severe	46 (88)	4 (100)	10 (91)	40 (89)	50 (89)
Target joints (maximum target joints = 12) ^b					
N of PWHA	43	4	8	39	47
Mean (range)	1.8 (0-7)	1.8 (0-3)	0.8 (0-2)	2 (0-7)	1.8 (0-7)
Median	1	2	1	2	1
Target joints affected, n of PWHA (%) ^{b,c}					
Shoulder	4/33 (12)	0/3 (0)	0/5 (0)	4/31 (13)	4/36 (11)
Elbow	10/33 (30)	0/3 (0)	0/5 (0)	10/31 (32)	10/36 (28)
Ankle	25/33 (76)	3/3 (100)	5/5 (100)	23/31 (74)	28/36 (78)
Hip	2/33 (6)	0/3 (0)	0/5 (0)	2/31 (6)	2/36 (6)
Knee	12/33 (36)	1/3 (33)	0/5 (0)	13/31 (42)	13/36 (36)

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Overall, the 3 most common reasons for switching from another rFVIII to rurioctocog alfa pegol were: 1) to reduce the number of infusions, 2) to reduce breakthrough bleeds, and 3) to improve treatment adherence (Figure 3). PWHA aged ≥ 12 years (n=45) had the same top 3 reasons for switching rFVIII as the overall population; however, for PWHA aged < 12 years (n=11), venous access issues were the second most common reason for switching to prophylactic rurioctocog alfa pegol (after reducing the number of infusions [patient and caregiver] and before improving adherence and reducing breakthrough bleeds).

Real-World Consumption of Prophylactic Rurioctocog Alfa Pegol

Data for the consumption of prophylactic rFVIII were available for 51 of 56 PWHA (Table 2). Five PWHA were excluded from this analysis because they had incomplete information on dosing or frequency of rFVIII therapy before receiving rurioctocog alfa pegol.

Before receiving rurioctocog alfa pegol, PWHA received prophylaxis with an SHL rFVIII for a median of 80.8 months (n=29; range=3.9-421.1; mean=109.4) or with an EHL rFVIII for a median of 13.5 months (n=4; range=3.0-28.0; mean=14.5; Appendix A, available in online article).

Overall, the median duration of rurioctocog alfa pegol therapy was 12 months (range=1.0-24.0 months; mean=12.2 months). PWHA who received prior therapy with an SHL rFVIII received rurioctocog alfa pegol for a median of 12 months (n=52; range=1-24; mean=12.4) or 10 months for EHL rFVIII (n=4; range=1-18; mean=9.8).

After switching to rurioctocog alfa pegol, PWHA experienced a significant reduction of 20.9% in the mean number of days per week of factor administered (from 2.7 to 2.2, $P<0.001$) in the overall population (Table 2). This reduction was significant for those PWHA who switched from an SHL rFVIII (23.1% reduction, $P<0.001$), but not for PWHA who switched from

TABLE 1 Patient Characteristics (continued)

Variable	Prior Prophylactic Therapy Group		Age Group		Total (N = 56)
	Prior SHL (n = 52)	Prior EHL (n = 4)	< 12 Years (n = 11)	≥ 12 Years (n = 45)	
Subjective pain, n of PWAH (%) ^b					
Mild	12 (23)	1 (25)	4 (36)	9 (20)	13 (23)
Mild to moderate	11 (21)	1 (25)	2 (18)	10 (22)	12 (21)
Moderate	11 (21)	2 (50)	0 (0)	13 (29)	13 (23)
Moderate to severe	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)
Severe	2 (4)	0 (0)	0 (0)	2 (4)	2 (4)
Not specified	15 (29)	0 (0)	5 (45)	10 (22)	15 (27)
Days active per week					
N of PWAH	42	4	7	39	46
Mean (range)	5.8 (1-7)	5.3 (1-7)	6.4 (3-7)	5.6 (1-7)	5.7 (1-7)
Patients by practice type, n (%)					
Academic	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)
Community	4 (8)	1 (25)	0 (0)	5 (11)	5 (9)
HTC—academic hospital	31 (60)	2 (50)	7 (64)	26 (58)	33 (59)
HTC—nonacademic hospital	12 (23)	1 (25)	3 (27)	10 (22)	13 (23)
Nonacademic hospital	4 (8)	0 (0)	1 (9)	3 (7)	4 (7)
Patient insurance, n (%)					
Commercial	24 (46)	2 (50)	3 (27)	23 (51)	26 (46)
Dual eligibility	2 (4)	0 (0)	0 (0)	2 (4)	2 (4)
Medicaid	16 (31)	2 (50)	8 (73)	10 (22)	18 (32)
Medicare	6 (12)	0 (0)	0 (0)	6 (13)	6 (11)
Other payer	4 (8)	0 (0)	0 (0)	4 (9)	4 (7)

^aData for the 4 U.S. states with the most PWHAs are shown; however, PWHAs came from across a total of 21 states. The other states include Alabama, Arizona, Florida, Hawaii, Idaho, Kentucky, Louisiana, Minnesota, Mississippi, Oregon, Pennsylvania, South Carolina, South Dakota, Tennessee, Utah, Virginia, and Washington.

^bThese data were collected at the time of rurioctocog alfa pegol therapy.

^cDenominator is patients with ≥ 1 target joint.

EHL = extended half-life; HTC = hemophilia treatment center; IQR = interquartile range; PWHAs = people with hemophilia A; SHL = standard half-life.

an EHL rFVIII (21.4% increase, $P=0.215$), although the latter population comprised only 4 PWHAs. There was no significant difference in the mean weekly rFVIII dose reported before and after switching to rurioctocog alfa pegol in the overall population or in the groups of PWHAs who received prior treatment with an SHL or EHL rFVIII.

The frequency of factor administration was comparable between the overall population and PWHAs aged ≥ 12 years, who had a significant 22.4% reduction in the mean number of days per week of factor consumption after switching to rurioctocog alfa pegol (from 2.7 to 2.1, $P=0.001$). The 14.3% reduction in the mean number of days per week of factor consumption after switching to rurioctocog alfa pegol in PWHAs aged < 12 years is interpreted with caution given the small sample size ($n=9$, $P=0.133$).

Also, in line with the overall population, the reduction in the mean number of days per week of factor administration was significant for those PWHAs aged ≥ 12 years who switched from an SHL rFVIII (25.2% reduction from 2.8 days per week to 2.1, $P<0.001$), but not for those PWHAs aged ≥ 12 years who switched from an EHL rFVIII (21.4% increase from 1.8 days per

week to 2.1, $P=0.215$). For PWHAs aged < 12 years, such a comparison could not be made between those who received a previous SHL or EHL rFVIII because no PWHAs aged < 12 years had received an EHL rFVIII before rurioctocog alfa pegol therapy.

While on rurioctocog alfa pegol therapy, minor breakthrough bleeds ($n=27$) were treated with a mean rurioctocog alfa pegol dose of 38.7 IU per kg (standard deviation [SD] = 12.0; median dose of 40 IU per kg, SD = 2.3). Moderate ($n=18$) and major bleeds ($n=21$) were treated with mean doses of 42.5 IU per kg (SD = 10.7; median dose = 50.0 IU per kg, SD = 2.5) and 46.2 IU per kg (SD = 17.3; median dose = 50.0 IU per kg, SD = 3.8), respectively. By comparison, for SHL rFVIII before switching treatment, a mean dose range of 25.0–45.0 IU per kg (SD = 7.1–16.0) and a median dose range of 25.0–50.0 IU per kg (SD = 2.4–8.0) was used to treat breakthrough bleeds, depending on the rFVIII product administered. Breakthrough bleeds treated with an EHL rFVIII ($n=4$) before switching required a mean dose of 44.8 IU per kg (SD = 14.0; median dose = 50.0 IU per kg, SD = 7.0). The amount of factor previously used to treat breakthrough bleeds was not reported by the type of bleed (e.g., minor, moderate, or major bleed).

FIGURE 2 rFVIII Replacement Therapy Before Switching to Rurioctocog Alfa Pegol

^aAntihemophilic factor (recombinant) single chain.

^bAntihemophilic factor (recombinant) Fc fusion protein.

EHL = extended half-life; PWHA = people with hemophilia A; rFVIII = recombinant factor VIII; SHL = standard half-life.

ABR on Prior Therapy and on Rurioctocog Alfa Pegol After Switching

ABR data before and after switching to rurioctocog alfa pegol were reported for 38 of 56 PWHA. Overall, there was a significant decrease in the mean ABR after switching to rurioctocog alfa pegol when compared with prior therapy, from 5.8 to 1.7 (overall reduction of 71%, $P < 0.001$; Table 2). PWHA who received prior therapy with an SHL rFVIII experienced a

significant 73% reduction in ABR after switching to rurioctocog alfa pegol (5.9 vs. 1.6, $n = 35$, $P < 0.001$). PWHA who received prior therapy with an EHL rFVIII also experienced a reduction in ABR after switching to rurioctocog alfa pegol, although this reduction was not significant (44% reduction, 4.7 vs. 2.6; $n = 3$, $P = 0.4$).

Of the 38 PWHA with bleeding data before and after switching to rurioctocog alfa pegol, 33 were aged ≥ 12 years. In this subgroup, the mean ABR decreased from 6.0 to 1.7 after switching to

TABLE 2 Comparisons of Frequency, Weekly Consumption, and Effectiveness of Prophylactic Factors

Total N of PWH A	Prior SHL				Prior EHL				Total Population			
	Prior Factor	Rurioctocog Alfa Pegol	% Change	P Value	Prior Factor	Rurioctocog Alfa Pegol	% Change	P Value	Prior Factor	Rurioctocog Alfa Pegol	% Change	P Value
	n = 47				n = 4				N = 51 ^a			
Frequency of treatment administration												
Mean days/week	2.8	2.2	-23.1	<0.001	1.8	2.1	+21.4	0.215	2.7	2.2	-20.9	<0.001
Factor consumption												
Overall mean weekly dose, IU/kg	109.8	100.6	-8.4	0.094	83.8	106.3	+26.9	0.239	107.8	101.0	-6.3	0.203
N of PWH A Aged ≥12 years	n = 38				n = 4				N = 42			
Frequency of treatment administration												
Mean days/week	2.8	2.1	-25.2	<0.001	1.8	2.1	+21.4	0.215	2.7	2.1	-22.4	0.001
Factor consumption												
Mean weekly dose, IU/kg	104.6	94.7	-9.5	0.135	83.8	106.3	+26.9	0.239	102.6	95.8	-6.7	0.275
N of PWH A Aged < 12 years	n = 9				n = 0				N = 9			
Frequency of treatment administration												
Mean days/week	2.8	2.4	-14.3	0.133	NA				2.8	2.4	-14.3	0.133
Factor consumption												
Mean weekly dose, IU/kg	131.8	125.6	-4.5	0.393	NA				131.8	125.6	-4.5	0.393
Total N of PWH A ^b	n = 35				n = 3				N = 38			
ABR												
Mean	5.9	1.6	-73	<0.001	4.7	2.6	-44	0.4	5.8	1.7	-71	<0.001
Median ^c	4.0	0.8	-80	NR	5.0	2.4	-52	NR	4.0	0.8	-80	NR
N of PWH A Aged ≥ 12 years	n = 30				n = 3				N = 33			
ABR												
Mean	6.2	1.6	-75	0.001	4.7	2.6	-44	0.4	6.0	1.7	-73	0.001
Median ^c	4.0	0.8	-81	NR	5.0	2.4	-52	NR	4.0	0.8	-80	NR
N of PWH A Aged < 12 years	n = 5				n = 0				N = 5			
ABR												
Mean ^d	4.0	1.8	-56	NR	NA				4.0	1.8	-56	NR
Total N of PWH A	n = 52				n = 4				N = 56			
Categorized bleeding events ABR (n of PWH A)												
ABR=0	7	19	+63	NR	0	1	+100	NR	7	20	+65	NR
ABR=1	1	15	+93	NR	1	1	0	NR	2	16	+87	NR
ABR=2	2	5	+60	NR	0	0	0	NR	2	6	+67	NR
ABR=3	10	5	-50	NR	1	0	-100	NR	11	5	-55	NR
ABR≥4	20	5	-75	NR	2	1	-50	NR	22	6	-73	NR

Note: Percentage differences may not exactly reflect the difference between the preswitch and postswitch values due to rounding.

^aFive PWHa were excluded from this analysis because they had incomplete information on dosing or frequency of rFVIII therapy before receiving rurioctocog alfa pegol.

^bBleed data available before and after switch to rurioctocog alfa pegol.

^cMedian ABRs were not tested for significant differences, as the analyses were performed on mean ABRs.

^dOnly the mean ABR was available for this data set.

ABR=annualized bleeding rate; EHL=extended half-life; NA=not available; NR=not reported; PWHa=people with hemophilia A; rFVIII=recombinant factor VIII; SHL=standard half-life.

rurioctocog alfa pegol (73% reduction, $P=0.001$). In the PWHa subgroup aged <12 years ($n=5$), the mean ABR decreased from 4.0 to 1.8 after switching to rurioctocog alfa pegol, representing a 56% reduction in ABR (P value not reported).

Of all 56 PWHa with any bleed data, 20 PWHa (36%) had no bleeding events after switching to rurioctocog alfa pegol, compared with 7 of 56 PWHa (13%) with no bleeding events before switching (Table 2).

FIGURE 3 Reasons for Switching to Rurioctocog Alfa Pegol

Note: Percentages are based on the number of PWHA or their caregivers rating the reason for switching as being important. Percentages within each subgroup do not equal 100% as PWHA or their caregivers could choose multiple reasons for switching to treatment with rurioctocog alfa pegol.

PWHA = people with hemophilia A.

Adherence to Therapy Before and After Switching to Rurioctocog Alfa Pegol

Data on overall adherence to prior rFVIII therapy were provided by all 56 PWHA (SHL rFVIII=52, EHL rFVIII=4). On prior rFVIII therapy, 68% (n=38/56) of PWHA reported good-to-complete adherence, 21% (n=12/56) indicated moderate adherence, and 9% (n=5/56) indicated poor adherence. For PWHA aged <12 years, 100% (n=11/11) indicated good-to-complete adherence to prior rFVIII therapy, and 60% (n=27/45) did so in the aged ≥12 years group (Appendix B, available in online article).

When assessed by prior rFVIII therapy, good-to-complete adherence was reported by 67% (n=35/52) of all PWHA who received prior SHL rFVIII and 79% (n=41/52) after they switched to rurioctocog alfa pegol. Good-to-complete adherence was reported by 3 of the 4 PWHA who received prior

EHL rFVIII and all 4 PWHA after switching to rurioctocog alfa pegol. In the <12 years age group overall, good-to-complete adherence was reported by 100% (n=11/11) of PWHA who received prior SHL or EHL rFVIII and 91% (n=10/11) after they switched to rurioctocog alfa pegol. For the ≥12 years age group overall, good-to-complete adherence was reported by 60% (27/45) of PWHA who received prior SHL or EHL rFVIII and 78% (35/45) after they switched to rurioctocog alfa pegol.

Discussion

This study represents the largest detailed evaluation of the real-world use of rurioctocog alfa pegol in PWHA following prior prophylaxis with other (SHL and EHL) rFVIII products. The effect of this switch in treatment on clinical outcomes (including ABR), treatment adherence, and factor consumption were all reported, along with the reasons for switching. A previous

retrospective chart review had shown a general improvement in bleeding control in patients who switched from SHL rFVIII to rurioctocog alfa pegol, with a lower infusion frequency and factor consumption in most patients; this study evaluated data from 15 patients, none of whom were previously treated with EHL rFVIII.²³ The ongoing international AHEAD study (NCT02078427) is assessing the natural history of hemophilia A and long-term outcomes in terms of effectiveness, safety, and quality of life in patients receiving rFVIII or rurioctocog alfa pegol in routine clinical practice across more than 20 countries.²⁴

The reduction of ABR is the most important goal of prophylaxis in HA. Clinical study data have shown that rurioctocog alfa pegol prophylaxis successfully reduces ABR in adults and children with previously treated HA (NCT01599819 and NCT01736475 [PROLONG-ATE]; NCT02210091).^{5,16} Real-world evidence suggests that initiating early prophylaxis may reduce the health care costs and long-term complications associated with bleeding events.²⁵ However, there is a paucity of research describing the patient experience and outcomes with EHL rFVIII outside of clinical trials. The current real-world study found that while receiving rurioctocog alfa pegol therapy, 39% of PWHAs (n=20/51) experienced no bleeding events. These data are somewhat lower than the real-world evidence previously reported by Dunn et al. (2018), which showed that 53% of PWHAs (n=8/15) experienced no bleeding events after switching to rurioctocog alfa pegol,³ although the current study includes a more heterogeneous pediatric population. Taken together, this shows that data for PWHAs treated with rurioctocog alfa pegol in routine clinical practice are consistent with data from the pivotal clinical studies.

In terms of factor consumption, the dose of EHL rFVIII is higher per infusion compared with SHL rFVIII. However, data from clinical trials indicate that overall consumption is similar for SHL and EHL rFVIII products.^{20,21} Data from the current study found that PWHAs who switched from an SHL rFVIII to rurioctocog alfa pegol reported lower mean dosing frequency and thus lower factor consumption with rurioctocog alfa pegol compared with their previous rFVIII. In the real-world study by Dunn et al., EHL rFVIII was shown to reduce factor consumption by 19% compared with SHL rFVIII therapy in patients with severe hemophilia A.³ Coupled with the improved ABR observed with rurioctocog alfa pegol versus prior therapies in the current study, this suggests that the health outcome changes due to switching treatment should be taken into account when considering EHL rFVIII consumption.

PWHAs who switched from an EHL rFVIII to rurioctocog alfa pegol (n=4) also experienced a reduction in ABR, although this was not significant ($P=0.4$). While this subgroup of PWHAs was too small to allow meaningful comparisons to be drawn, there were trends toward clinical improvement with rurioctocog alfa pegol treatment versus prior EHL rFVIII. However, further work is needed to confirm this hypothesis.

In terms of treatment adherence, good-to-complete adherence to the rurioctocog alfa pegol prophylactic regimen was reported by 79% (n=41/52) and 100% (n=4/4) of all PWHAs who switched from a prior SHL and EHL rFVIII, respectively. These rates are higher than the reported 53% of patients who adhered to both their prescribed frequency of administration for >80% of study weeks and $\geq 80\%$ of their prescribed FVIII doses in a separate non-interventional, prospective study of PWHAs without inhibitors (n=41 on SHL and n=9 on EHL FVIII). Patient survey data show that the time-consuming nature of some prophylactic rFVIII regimens is the most prominent barrier to treatment adherence.^{7,8,26} Data from the current study indicate that rurioctocog alfa pegol has a lower treatment burden versus SHL rFVIII. Lowering treatment burden by reducing the number of infusions and breakthrough bleeds were reported to be among the most common reasons for PWHAs to switch to rurioctocog alfa pegol in the current study. These findings are supported by the study by Dunn et al., in which the most frequently reported reason for switching to rurioctocog alfa pegol was to reduce infusion frequency (14/15 PWHAs).³ However, it should be considered that the decision to switch treatments may also have been influenced by the treating physician.

Limitations

The limitations of this study are typical of retrospective observational studies in the real-world setting. PWHAs were not randomized and observers were not blinded. The source data, which are from 3 specialty pharmacies, may not be representative of all PWHAs in the United States. Also, as some subgroups (e.g., PWHAs aged <12 years, PWHAs treated with a prior EHL rFVIII) were small in sample size, these results should be interpreted with caution. Bleeding rates were reported by patients, 3 PWHAs did not report their bleeding rates on rurioctocog alfa pegol, and the effect of the physician-patient relationship in the decision to switch rFVIII therapies could not be assessed. Follow-up was for 6-12 months, as lengthier follow-up can be a challenge, although this duration of time is typical for treatment of hemophilia patients in randomized clinical trials. An assessment of therapy cost was not included in this analysis.

Conclusions

These real-world data show that switching from an SHL rFVIII to rurioctocog alfa pegol reduced ABR, without increasing factor dosing frequency or consumption, while also positively influencing treatment adherence. Reducing the treatment burden associated with SHL rFVIII is the major factor driving PWHAs to switch to rurioctocog alfa pegol. These real-world data are consistent with the results of the pivotal clinical trials where rurioctocog alfa pegol was shown to have a positive clinical effect on ABR. The results of this study highlight rurioctocog alfa pegol as an important additional option for the care of PWHAs.

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DISCLOSURES

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APPENDIX A Months on Prophylactic rFVIII Before and on Rurioctocog Alfa Pegol

Months on Prophylactic rFVIII Before Rurioctocog Alfa Pegol	Prior Prophylactic Therapy Group		Age Group		Total (n = 33)
	Prior SHL (n = 29)	Prior EHL (n = 4)	< 12 Years (n = 6)	≥ 12 Years (n = 27)	
Mean	109.4	14.5	78.0	102.3	97.9
Median (range)	80.8 (3.9-421.1)	13.5 (3.0-28.0)	82.3 (44.0-112.8)	71.9 (3.0-421.1)	71.9 (3.0-421.1)
Months on Rurioctocog Alfa Pegol	Prior Prophylactic Therapy Group		Age Group		Total (n = 56)
	Prior SHL (n = 52)	Prior EHL (n = 4)	< 12 years (n = 11)	≥ 12 years (n = 45)	
Mean	12.4	9.8	10.4	12.7	12.2
Median (range)	12.0 (1.0-24.0)	10.0 (1.0-18.0)	9.0 (1.0-24.0)	14.0 (1.0-24.0)	12.0 (1.0-24.0)

EHL = extended half-life; rFVIII = recombinant factor VIII; SHL = standard half-life.

APPENDIX B Adherence to Prior Prophylactic Factor and Rurioctocog Alfa Pegol

Adherence Assessment ^a	Prior Prophylactic Therapy Group						Total
	Prior SHL			Prior EHL			
	< 12 Years	≥ 12 Years	All	< 12 Years	≥ 12 Years	All	
Adherence to prior prophylactic factor, n (%)							
N of PWHA	11	41	52	0	4	4	56
Poor adherence	0 (0)	5 (12)	5 (10)	0 (0)	0 (0)	0 (0)	5 (9)
Moderate adherence	0 (0)	11 (27)	11 (21)	0 (0)	1 (25)	1 (25)	12 (21)
Good adherence	2 (18)	17 (41)	19 (37)	0 (0)	1 (25)	1 (25)	20 (36)
Complete adherence	9 (82)	7 (17)	16 (31)	0 (0)	2 (50)	2 (50)	18 (32)
Adherence not specified	0 (0)	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)
Adherence to ruriotocog alfa pegol, n (%)							
N of PWHA	11	41	52	0	4	4	56
Poor adherence	0 (0)	3 (7)	3 (6)	0 (0)	0 (0)	0 (0)	3 (5)
Moderate adherence	0 (0)	7 (17)	7 (13)	0 (0)	0 (0)	0 (0)	7 (13)
Good adherence	2 (18)	18 (44)	20 (38)	0 (0)	2 (50)	2 (50)	22 (39)
Complete adherence	8 (73)	13 (32)	21 (40)	0 (0)	2 (50)	2 (50)	23 (41)
Adherence not specified	1 (9)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)

^aOrdinal treatment adherence based on a subjective assessment as perceived by people with hemophilia A. For prescriptions filled, 100% is complete adherence, 80%-99% is good adherence, 50%-79% is moderate adherence, and <50% is poor adherence.

EHL = extended half-life; SHL = standard half-life.