Comparing Factor Use and Bleed Rates in U.S. Hemophilia A Patients Receiving Prophylaxis with 3 Different Long-Acting Recombinant Factor VIII Products

Mindy L. Simpson, MD; Vidhi Desai, MD; Géraldine S. Maro, PhD; and Songkai Yan, MS

ABSTRACT

BACKGROUND: Recombinant factor VIII (rFVIII) products have been developed with improved pharmacokinetics, offering some patients the potential to extend dosing intervals, thereby reducing their dosing frequency while minimizing the occurrence of bleeding events. No clinical trials have been conducted to compare the bleeding rates and use of these long-acting products.

OBJECTIVES: To (a) assess real-world use of prophylaxis regimens in patients using 1 of 3 different long-acting products—rVIII-SingleChain, rFVIII-Fc, or PEG-rFVIII; and (b) compare bleeding rates, dosing frequency, and factor consumption in 3 cohorts of patients. For rVIII-SingleChain patients, these measures were also compared with the prior products these patients used.

METHODS: De-identified patient chart data were collected from 11 hemophilia treatment centers in the United States. Patients were included if they had been treated with rVIII-SingleChain, rFVIII-Fc, or PEG-rFVIII prophylaxis for ≥ 8 weeks at the time of data collection. Matching for age and disease severity was attempted between the 3 patient groups. Data were also collected for patients who switched from their prior FVIII product to prophylaxis with rVIII-SingleChain.

RESULTS: Data were obtained for 120 male patients. The majority of patients were dosing 2 times per week or less frequently (rVIII-SingleChain 65.0%, rFVIII-Fc 70.0%, and PEG-rFVIII 72.5%). Annualized bleeding rates were comparable among the 3 cohorts, with median (mean) values of 2.0 (2.6) with rVIII-SingleChain and rFVIII-Fc, and 3.0 (3.7) with PEG-rFVIII. The overall median (mean) FVIII consumption in IU per kg per week (IU/kg/week) was 91.9 (91.1) with rVIII-SingleChain, 108.5 (103.6) with rFVIII-Fc, and 97.6 (111.0) with PEG-rFVIII, resulting in expected mean annual consumption of 322,140 IU, 361,816 IU, and 373,100 IU, respectively, for a 70 kg patient aged ≥ 12 years. The mean consumption was significantly different among the 3 products for all patients ($P=0.0164$) and for those dosed 2 times per week ($P<0.0001$). Among patients infusing 2 times per week, median (mean) consumption with rVIII-SingleChain was 83.8 (81.2) IU/kg/week, compared with 109.6 (104.4) IU/kg/week for rFVIII-Fc and 92.1 (91.5) IU/kg/week for PEG-rFVIII. Additionally, switching from prophylaxis with prior FVIII products to rVIII-SingleChain increased the proportion of patients dosing ≤ 2 times per week (20% to 65%), decreased mean consumption (103.3 to 91.9 IU/kg/week; $P=0.0164$), and maintained the mean annualized bleeding rates (2.9 to 2.6; $P=0.5665$).

CONCLUSIONS: Results for rVIII-SingleChain confirm the findings from its pivotal trial. Analyses of annualized bleeding rates demonstrate comparable clinical outcomes of rVIII-SingleChain to the other 2 long-acting products assessed. In patients aged ≥ 12 years, rVIII-SingleChain prophylaxis may result in an 11.0% and 13.7% lower mean factor consumption than rFVIII-Fc and PEG-rFVIII, respectively, representing a potential cost-saving opportunity of 34% in both cases—at the current wholesale acquisition cost of

the corresponding products. In addition, in patients using rVIII-SingleChain prophylactically, consumption was reduced compared with their prior products, while bleeding control was well maintained.

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What is already known about this subject

- Emerging novel therapies have significantly changed the landscape of hemophilia A treatment.
- In the United States, numerous plasma-derived factor VIII (FVIII) and recombinant FVIII (rFVIII) products are available to treat hemophilia A.
- Long-acting rFVIII products allow treatment intervals to be extended, thereby enabling a reduction in the burden of treatment.

What this study adds

- This research presents the first real-world analysis comparing 3 long-acting rFVIII products.
- The results of this analysis demonstrate that prophylaxis with rVIII-SingleChain had lower mean factor consumption than both rFVIII-Fc and PEG-rFVIII, with comparable bleed rates.

Hemophilia A is a rare, X-linked genetic disorder occurring in approximately 1 in 10,000 births.¹ Approximately 70% of patients with hemophilia A inherit the condition; however, 30% of patients have no family history of hemophilia and develop the condition because of a spontaneous mutation in the coagulation factor VIII (FVIII) gene.² These inherited or spontaneous mutations result in an absence or deficiency of FVIII leading to abnormal or uncontrolled bleeding episodes, the severity of which are dependent on residual circulating factor levels. In patients with severe hemophilia A (defined as FVIII activity level $< 1\%$), continuous prophylaxis with an FVIII product is the standard of care.^{1,3,4} The goal of prophylaxis is to prevent spontaneous bleeding, particularly bleeding into the joints, and it has been shown to reduce the development of joint arthropathy and subsequent disability as well as improve overall health and quality of life.^{5,6}

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The landscape of hemophilia A treatment has changed significantly with emerging novel therapies. Numerous plasma-derived FVIII and recombinant FVIII (rFVIII) products are available to treat hemophilia A in the United States, and while prophylaxis with these products has demonstrated a clear benefit in patients, including reduced spontaneous bleeding and prolonged joint health, there are still challenges.⁷ In particular, in patients treated with prophylaxis, using standard half-life (SHL) rFVIII products typically requires 3-4 infusions per week, and the frequency of infusions may affect patient compliance.⁸ Although prophylaxis is effective, it does not completely prevent joint disease, and patients may still experience breakthrough bleeding. In addition, some patients may have difficulties with venous access, which may be associated with an increase in the overall burden of prophylaxis treatment.⁹

To address the burden of prophylaxis, several rFVIII products with a prolonged half-life and improved pharmacokinetic (PK) profiles have been developed in recent years using single-chain technology as well as Fc fusion and PEGylation.¹⁰⁻¹² Clinical trials have shown that rVIII-SingleChain (AFSTYLA, CSL Behring), rFVIII-Fc (Eloctate, Bioverativ), and PEG-rFVIII (Adynovate, Takeda) are effective for the treatment and prevention of bleeds and offer dosing regimens that can be tailored to the individual needs of the patient by increasing/decreasing the infusion frequency or dose to maintain FVIII activity levels >1%, as recommended by the World Federation of Hemophilia.^{1,13-17} Importantly, the introduction of long-acting rFVIII products allows for some patients to reduce their dosing frequency, which may help decrease the burden of treatment.^{18,19} Allowing some patients to have substantially fewer infusions per year (e.g., switching from a regimen of 3 times per week to 2 times per week can result in up to 52 fewer infusions per year) can be critical for patients who struggle with venous access and also help improve treatment compliance.¹⁹ Although currently there is no universal definition of an extended half-life (EHL) product, a recent review of the current evidence proposed 3 criteria for classifying EHL products.¹² Here, the authors concluded that rFVIII-Fc and PEG-rFVIII meet the criteria, whereas rVIII-SingleChain does not. However, as rVIII-SingleChain partially met these criteria, it cannot be concluded that rVIII-SingleChain is bioequivalent to SHL products, and others have noted that rVIII-SingleChain has an EHL compared with SHL FVIII products.^{12,20}

In addition to efficacy, another important consideration is the factor consumption when evaluating the overall benefit associated with any given product. While it is not a direct outcome of treatment, consumption of units in conjunction with bleed rates may provide a more comprehensive evaluation of treatment effectiveness, showing that patients can achieve similar bleed rates with a reduction in FVIII consumption.²¹ Indeed, an indirect comparison of clinical trials showed patients using a long-acting rFVIII product were able to reduce their FVIII

TABLE 1 Patient Characteristics

	rVIII-Single-Chain (n = 40)	rFVIII-Fc (n = 40)	PEG-rFVIII (n = 40)
Age, mean (SD)	28.7 (16.1)	30.8 (15.1)	30.5 (11.3)
Age group, n (%)			
Adult/adolescent (≥ 12 years)	35 (87.5)	35 (87.5)	38 (95.0)
Pediatric (< 12 years)	5 (12.5)	5 (12.5)	2 (5.0)
Weight (kg), mean (SD)	60.3 (18.0)	72.3 (24.9)	82.3 (28.8)
Disease severity, n (%)			
Severe	35 (87.5)	33 (82.5)	35 (87.5)
Mild/moderate	5 (12.5)	7 (17.5)	5 (12.5)
Duration of observation (weeks), mean (range)	43 (16-97)	52 (52-52)	52 (52-52)

SD = standard deviation.

consumption compared with using SHL FVIII therapy.⁹ Therefore, if reduced consumption is realized in clinical practice, then long-acting products have the potential to improve the management of hemophilia by reducing treatment burden and improving patient quality of life. Also important, if the price is the same or lower, reducing consumption will lead to the reduction of the associated costs of treatment. Here, we investigated the real-world use of prophylaxis regimens with rVIII-SingleChain, rFVIII-Fc, and PEG-rFVIII in patients with hemophilia A in the United States and compared factor consumption and bleeding rates in 3 cohorts. In addition, in patients receiving prophylaxis with their prior FVIII product who then switched to prophylaxis with rVIII-SingleChain, we compared bleeding rates, dosing frequency, and factor consumption.

Methods

Cohort Analysis

De-identified data were provided by treating physicians through retrospective review of pre-existing patient medical records from 11 hemophilia treatment centers across the United States for 120 hemophilia A patients. To be included, patients needed to be currently receiving prophylaxis for at least 8 weeks with 1 of 3 long-acting products available as of May 2017—rVIII-SingleChain, rFVIII-Fc, or PEG-rFVIII. The study was submitted to an institutional review board (IntegReview) and was determined to be exempt under category 4: secondary research for which consent is not required. Data were collected from May 2018 through July 2018, and for up to 3 years of prior treatment for patients treated with rVIII-SingleChain; a minimum of 8 weeks of treatment were required for patients to be included in the analysis. Data collected pertaining to patient characteristics, treatment, and clinical outcomes included age, weight, sex, severity of hemophilia A, duration on FVIII product, dosing (dose and frequency) of FVIII products, and number of spontaneous and traumatic bleeds reported over a period

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TABLE 2 Bleeding Rates with Long-Acting rFVIII Products

	rVIII-SingleChain	rFVIIIIFc	PEG-rFVIII	P Value
ABR	n=40	n=40	n=40	
Median (IQR)	2.0 (0.5-3.75)	2.0 (1.0-3.5)	3.0 (1.0-4.5)	
Mean (SD)	2.6 (2.8)	2.6 (2.8)	3.7 (4.4)	0.3814
Patients with 0 bleeds, n (%)	10 (25.0)	9 (22.5)	7 (17.5)	0.7883
2×/week	n=22	n=14	n=29	
Median (IQR)	1.5 (0.0-3.0)	1.0 (0.0-2.0)	3.0 (2.0-4.0)	
Mean (SD)	2.3 (2.9)	2.0 (2.9)	3.2 (2.7)	0.3401
Patients with 0 bleeds, n (%)	7 (31.8)	6 (42.9)	4 (13.8)	0.0993
3×/week	n=14	n=9	n=6	
Median (IQR)	3.0 (1.0-4.0)	2.0 (1.0-5.0)	4.0 (3.0-7.0)	
Mean (SD)	3.2 (3.1)	3.1 (3.0)	7.2 (8.5)	0.1926
Patients with 0 bleeds, n (%)	3 (21.4)	2 (22.2)	0 (0.0)	0.6689

ABR=annualized bleeding rate; IQR=interquartile range; SD=standard deviation.

of up to 12 months. Where possible, patient selection took into account age and disease severity in order to include similar patients (with respect to these variables) across patients using the 3 different products. Both adult and pediatric patients were included; for the purposes of this study, patients aged ≥ 12 years were defined as adult/adolescent, and patients aged < 12 years were defined as pediatric, as per the prescribing information for each product. In addition, patients with $< 1\%$ of normal FVIII activity blood levels were defined as severe, patients with 1% to $\leq 5\%$ were defined as moderate, and patients with $> 5\%$ to 40% were defined as mild.

Data were analyzed and compared among patients using the 3 long-acting rFVIII products. The primary outcome measures were annualized bleeding rates (ABR, calculated by annualizing the number of bleeds based on the duration within which the bleeds occurred) and FVIII consumption. Prescribed dosing and infusion frequencies were taken from the most recent prescription of each product. Prophylactic factor consumption was normalized by multiplying the dose per infusion by number of infusions per week and dividing by the patient's weight, reported as IU per kg per week (IU/kg/week).

Switch Analysis

For patients receiving rVIII-SingleChain described in the cohort analysis above, data were also collected about the products they used before switching to rVIII-SingleChain. ABR, dosing frequency, and factor consumption were then compared between rVIII-SingleChain and previous products, using the same methods as in the cohort analysis.

Statistical Analysis

In the cohort analysis, differences in the ABR across brands were tested for statistical significance using analysis of covariance (ANCOVA) models that included age, weight, severity, and consumption as covariates. Likewise, statistical

significance of the differences in consumption was tested with ANCOVA models that controlled for age, weight, and severity. Fisher's exact test was used to assess if the differences in the percentage of patients with 0 bleeds for each brand were statistically significant.

Statistical tests performed for the switch analysis included paired t-tests to assess the observed differences in the ABR and consumption between rVIII-SingleChain and prior products. The statistical significance of the difference in the percentage of patients with 0 bleeds while on rVIII-SingleChain versus prior products was evaluated with McNemar's test.

Results

Cohort Analysis

A total of 120 male patients were included, with 40 patients using each product; patient characteristics are described in Table 1. The majority of patients were adult patients (108/120 [90%]), and most patients had severe hemophilia A (103/120 [85.8%]). Across all products, prophylaxis frequency was 2 times per week or fewer in the majority of patients (rVIII-SingleChain 65.0%, rFVIIIIFc 70.0%, and PEG-rFVIII 72.5%; Appendix A, available in online article).

Overall, median (mean) ABR values were 2.0 (2.6), 2.0 (2.6), and 3.0 (3.7) for rVIII-SingleChain, rFVIIIIFc, and PEG-rFVIII, respectively (Table 2). During the reporting period, the proportion of patients with 0 bleeds was similar for rVIII-SingleChain (25%) and rFVIIIIFc (22.5%), while a slightly lower proportion of those receiving PEG-rFVIII achieved 0 bleeds (17.5%). However, the differences among the 3 proportions were not statistically significant ($P=0.788$). When further analyzed by dosing frequency of 2 times per week and 3 times per week, ABRs observed were in general similar to the overall analysis (Table 2).

In the subgroup of patients with severe disease (data not shown), median (mean) ABR values were 2.0 (2.5) for

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TABLE 3 Factor Consumption with Long-Acting rFVIII Products

Consumption (IU/kg/week)	rVIII-SingleChain	rFVIIIIFc	PEG-rFVIII	P Value
Total	n = 40	n = 40	n = 40	
Median (min-max)	91.9 (16.9-163.9)	108.5 (15.2-176.7)	97.6 (51.3-414.8)	0.0164
Mean (SD)	91.1 (32.8)	103.6 (41.2)	111.0 (60.4)	
IQR	65.1-117.4	71.9-134.9	86.1-118.4	
2×/week	n = 22	n = 14	n = 29	
Median (min-max)	83.8 (41.7-101.5)	109.6 (48.2-137.5)	92.1 (51.3-130.4)	<0.0001
Mean (SD)	81.2 (17.9)	104.4 (22.7)	91.5 (20.9)	
IQR	64.5-100.0	97.3-115.8	82.8-103.4	
3×/week	n = 14	n = 9	n = 6	
Median (min-max)	119.6 (65.7-163.9)	154.7 (121.7-176.7)	127.1 (100.1-159.1)	0.0433
Mean (SD)	121.9 (24.5)	151.4 (17.8)	128.8 (22.7)	
IQR	117.1-130.6	140.8-161.5	112.8-146.6	

IQR=interquartile range; SD=standard deviation.

rVIII-SingleChain (n = 35), 2.0 (2.8) for rFVIIIIFc (n = 33), and 3.0 (3.9) for PEG-rFVIII (n = 35). Patients on a 2 times per week or 3 times per week dosing regimen demonstrated similar ABR results compared with those reported across all dosing frequencies combined. In patients with severe disease dosing 2 times per week, median (mean) ABRs were 1.5 (2.3) for rVIII-SingleChain, 1.0 (2.2) for rFVIIIIFc, and 3.0 (3.3) for PEG-rFVIII. In patients dosing 3 times per week, they were 2.0 (3.1) for rVIII-SingleChain and rFVIIIIFc, and 4.0 (7.2) for PEG-rFVIII.

The mean overall consumption across all dosing frequencies by IU/kg/week was 91.1 with rVIII-SingleChain, 103.6 with rFVIIIIFc, and 111.0 with PEG-rFVIII ($P=0.0164$; Table 3). Among patients infusing 2 times per week ($P<0.0001$) or 3 times per week ($P=0.0433$), mean consumption was also lower with rVIII-SingleChain than with rFVIIIIFc or PEG-rFVIII. In patients treated with rVIII-SingleChain on a regimen of 2 times per week, consumption was roughly two thirds of that for those on a regimen of 3 times per week (median [mean] of 83.8 [81.2] vs. 119.6 [121.9] IU/kg/week, respectively). Similar ratios between the 2 dosing regimens were observed for rFVIIIIFc or PEG-rFVIII as well.

In patients ≥ 12 years of age, the overall median (mean) consumption for rVIII-SingleChain (n = 35), rFVIIIIFc (n = 35), and PEG-rFVIII (n = 38) was 87.7 (88.5), 99.4 (99.4), and 97.3 (102.5) IU/kg/week, respectively. In patients < 12 years of age, the median (mean) consumption for rVIII-SingleChain (n = 5), rFVIIIIFc (n = 5), and PEG-rFVIII (n = 2) was 100.0 (108.9), 122.0 (132.9), and 272.6 (272.6) IU/kg/week, respectively. In patients with severe disease, overall mean consumption for rVIII-SingleChain (n = 35), rFVIIIIFc (n = 33), and PEG-rFVIII (n = 35) was 90.1, 107.8, and 118.6 IU/kg/week, respectively; $P<0.01$ (Figure 1). Of which, patients infusing 2 times per week had mean consumption using rVIII-SingleChain (n = 22) of 81.2 IU/kg/week compared with 106.7 IU/kg/week with

rFVIIIIFc (n = 12) and 98.4 IU/kg/week with PEG-rFVIII (n = 24; $P=0.0001$). Similarly, in patients on a dosing regimen of 3 times per week, mean consumption was lower with rVIII-SingleChain (125.8 IU/kg/week, n = 10) than with either rFVIIIIFc or PEG-rFVIII (151.4 IU/kg/week, n = 9; and 128.8 IU/kg/week, n = 6, respectively; $P=0.0561$).

Switch Analysis

In patients receiving rVIII-SingleChain, ABR and consumption were compared while they were on their prior FVIII product before switching to rVIII-SingleChain. Of the patients also on prophylaxis before switching to rVIII-SingleChain (prophylaxis-to-prophylaxis comparison, n = 39), 94.9% (37/39) patients were using SHL products and 5.1% (2/39) were using long-acting products. Before the switch, the majority of patients had a dosing regimen of 3 times per week (79.4%), with only 10.3% dosing 2 times per week; however, after switching to rVIII-SingleChain, the percentage of patients dosing 2 times per week increased to 53.8% (Appendix B, available in online article). In addition, all patients (10.3%) who were dosing once per week were able to maintain this dosing frequency after switching to rVIII-SingleChain. The 4 patients on once-per-week dosing were aged 18-36 years. Their ABR (mean/median) before and after switching to rVIII-SingleChain was 3.3/3.0 and 1.9/1.5, respectively, and their consumption was 44.2/44.4 IU/kg and 37.7/41.5 IU/kg, respectively.

The overall ABR was comparable between prior FVIII products and rVIII-SingleChain, and this was consistent across dosing frequencies (Table 4). In addition, more patients experienced 0 bleeds after switching to rVIII-SingleChain, 25.6% compared with 7.7% with the prior FVIII product ($P=0.0001$). The corresponding percentages for spontaneous and traumatic bleeds were 17.9% versus 43.6% ($P=0.0321$) and 48.7% versus 51.3% ($P=1.0000$). For patients also on prophylaxis with their prior therapy, switching to rVIII-SingleChain prophylaxis

FIGURE 1 Overall Consumption for Patients with Severe Disease Receiving Prophylaxis by FVIII Replacement Product

Note: Values and x marks indicate means ($P < 0.01$). Whiskers indicate values within the minimum-maximum range. Green zone indicates second quartile range (25th-50th percentile). Blue zone indicates third quartile (50th-75th percentile).

resulted in a reduction in mean consumption across dosing frequencies, with a mean consumption of 103.3 IU/kg/week with prior FVIII product and 91.9 IU/kg/week with rVIII-SingleChain ($P = 0.0164$). Among these patients ($n = 39$), 32 decreased consumption after switching to rVIII-SingleChain, 6 increased, and 1 remained the same. Of the 21 patients on a regimen of 2 times per week with rVIII-SingleChain, mean weekly consumption reduced from 102.5 IU/kg/week to 82.2 IU/kg/week ($P = 0.0001$) when switching from prior FVIII to rVIII-SingleChain. Of these 21 patients, 19 decreased consumption after switching to rVIII-SingleChain, 1 increased, and 1 remained the same.

Discussion

This retrospective patient chart review provides real-world data on the use and effectiveness of long-acting FVIII products in the United States. The results of this analysis show that rVIII-SingleChain had lower mean consumption than either rFVIII-Fc or PEG-rFVIII, with comparable bleed rates.

With all 3 long-acting products, the majority of patients in this study were dosed ≤ 2 times per week (rVIII-SingleChain 65.0%, rFVIII-Fc 70.0%, and PEG-rFVIII 72.5%). In addition, ABRs were similar between products and were generally consistent with previously reported median ABRs of 1.14 for rVIII-SingleChain,¹³ 3.6 for rFVIII-Fc,¹⁵ and 3.7 for PEG-rFVIII.¹⁴ More frequent dosing (e.g., 3 times per week vs. 2 times per week) usually leads to more factor consumption,

and it is noted that patients treated on a regimen of 3 times per week had somewhat higher ABRs than those on 2 times per week. One possible explanation is that patients with more challenging clinical profiles (e.g., high bleeders) may be treated on a regimen of 3 times per week in order to best control bleeds. Furthermore, 25% of patients treated with rVIII-SingleChain achieved 0 bleeds, compared with 22.5% with rFVIII-Fc and 17.5% with PEG-rFVIII. In the switch analysis for rVIII-SingleChain, the number of patients achieving 0 bleeds was shown to be more than 3 times higher (25.6% vs. 7.7%) with rVIII-SingleChain than with prior therapy (predominantly SHL FVIII). In addition, 4 patients who were treated once per week with their prior product were able to maintain their bleeding control with lower consumption after switching to rVIII-SingleChain with the same dosing frequency.

The mean overall consumption by IU/kg/week for patients ≥ 12 years of age, across all dosing frequencies, was 88.5 with rVIII-SingleChain, 99.4 with rFVIII-Fc, and 102.5 with PEG-rFVIII, resulting in an expected overall mean annual consumption of 322,140 IU, 361,816 IU, and 373,100 IU, respectively, for a 70 kg patient. Using the respective wholesale acquisition cost obtained from Medi-Span PriceRx database (\$1.65, \$2.23, and \$2.16 per IU), the expected annual costs are \$531,531, \$806,850, and \$805,896, respectively. This may represent an example of the weight more typical for an adult and a different value for weight may be used for the calculations of the expected annual consumption and cost. We noted higher consumption in

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TABLE 4 Bleeding Rates in Prophylaxis-to-Prophylaxis Patients Currently Using rVIII-SingleChain Compared with Prior FVIII

ABR	Prior FVIII	rVIII-Single-Chain	P Value
Total (n = 39)			
Median (IQR)	2.0 (1.0-4.0)	2.0 (0.5-3.8)	
Mean (SD)	2.9 (2.4)	2.6 (2.9)	0.5665
Patients with 0 bleeds, n (%)	3 (7.7)	10 (25.6)	0.0001
2×/week (n = 21)			
Median (IQR)	2.0 (1.0-3.0)	1.0 (0.0-3.0)	
Mean (SD)	2.3 (1.4)	2.3 (2.9)	0.9366
Patients with 0 bleeds, n (%)	1 (4.8)	7 (33.3)	0.0124
3×/week (n = 14)			
Median (IQR)	3.0 (1.0-6.0)	3.0 (1.0-4.0)	
Mean (SD)	3.6 (3.6)	3.2 (3.1)	0.7420
Patients with 0 bleeds, n (%)	2 (14.3)	3 (21.4)	0.0201

ABR = annualized bleeding rate; IQR = interquartile range; SD = standard deviation.

pediatric patients <12 years. However, as shown in Table 1, pediatric patients constituted a very small percentage of all patients and were not representative of the overall sample. When these pediatric patients were excluded, the consumption was slightly reduced for all 3 products. Among patients infusing 2 times per week or less, median (mean) rVIII-SingleChain consumption (83.8 [81.2] IU/kg/week) was lower than with rFVIIIc (109.6 [104.4] IU/kg/week), and lower than with PEG-rFVIII (92.1 [91.5] IU/kg/week). In addition, rVIII-SingleChain consumption in patients on a regimen of 2 times per week was roughly two thirds of that for those on a regimen of 3 times per week (median [mean] of 83.8 [81.2] vs. 119.6 [121.9] IU/kg/week, respectively; Table 3). Similar ratios between the 2 dosing regimens were observed for rFVIIIc or PEG-rFVIII as well.

Furthermore, in the switch analysis, prophylaxis-to-prophylaxis patients (n = 18) switching from a dosing regimen of 3 times per week with prior FVIII to 2 times per week with rVIII-SingleChain demonstrated a reduction in consumption by approximately 23%. This may be crucial in reducing the burden of disease in a substantial proportion of patients as this could result in approximately 52 fewer infusions per year without any necessity to increase dose per infusion. In contrast, a recent study showed a higher consumption and expenditure over 2 years in patients who had switched from an SHL product to an EHL product; however, it is important to note that this analysis did not include rVIII-SingleChain, and it was not clear whether it included patients who switched from on-demand treatment to prophylaxis. In addition, the prophylactic dosing frequency used for this comparison was not reported.²²

Results for rVIII-SingleChain presented in this analysis confirm the findings of its pivotal trial and demonstrate comparable clinical outcomes such as well-maintained

bleeding control.¹³ The use of long-acting products, such as rVIII-SingleChain, could simplify the prophylactic regimens in some patients with hemophilia A by reducing the infusion frequency. This can reduce the burden associated with prophylactic treatment and, as such, make treatment more tolerable, and it may increase adherence in some patients.

The management of patients with hemophilia should be based on an individual's lifestyle and their PK parameters in order to provide an optimal treatment approach.²³ With the introduction of long-acting products, it is important to consider tailoring treatment using PK-guided dosing.^{24,25} Individualized prophylaxis regimens that reduce injection frequency and FVIII consumption can minimize the burden of treatment while maintaining excellent prophylactic efficacy.²⁶ Adherence to treatment is an important factor in reducing the number of breakthrough bleeds on prophylaxis, and this may improve the cost-effective use of prophylaxis. Further analyses may be needed in larger sample sizes to confirm the real-world experience and identify treatment patterns in patients with hemophilia A.

Limitations

Limitations of this current analysis include the small sample size and the relatively short period of assessment. Potential selection bias may be present in the sample, and we are not able to assess the effect of potentially differing patient management practices from the centers contributing data. As such, these results may not provide an overall representation of the entire patient population. In addition, the lack of information about the location, severity, treatment, and outcomes of bleeding events, as well as lack of adjustment of patient activity level and characteristics before initiating the studied products, have also limited the analysis.

Furthermore, it is important to note that measuring compliance to record actual consumption is difficult and our consumption calculations are based on the prescribing information; we acknowledge that this may not reflect the true factor consumption. However, given that the ABR was comparable to that reported in previous studies and the population is likely to include overusers and underusers, we believe it is reasonable to assume that the consumption calculations are a good estimate of the real-world use of FVIII products. The reason for switching to rVIII-SingleChain was not reported and potential selection bias from the centers contributing data may limit generalizing the patient population as a whole.

Finally, another weakness that we recognize is that, as the mean duration of observation for rVIII-SingleChain was shorter than the other 2 products (43 weeks vs. 52 weeks), the percentage of patients with no bleeds may be slightly higher than observed if the duration of observation was the same. While acknowledging the limitations in this study, the results presented here are consistent with the experience of

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rVIII-SingleChain clinical trials, demonstrating reduced consumption with longer dosing intervals while maintaining bleed control in the majority of patients.

Conclusions

This is the first real-world data analysis to compare the clinical benefits of long-acting products. This analysis demonstrated that in patients ≥ 12 years of age, rVIII-SingleChain may offer an 11.0% and 13.7% lower overall mean factor consumption than rFVIII-Fc and PEG-rFVIII, respectively (34% lower annual cost in both cases, based on current wholesale acquisition cost), while providing comparable bleed rates. Long-acting products allow some patients to be switched to a less-frequent dosing regimen, which can potentially reduce the burden of disease related to treatment intensity. This real-world data analysis suggests that among the long-acting products assessed, rVIII-SingleChain represents a product that potentially offers a reduction in the burden of disease, while maintaining desired clinical outcome, and an opportunity for cost saving.

Authors

MINDY L. SIMPSON, MD, *Pediatric Hematology/Oncology, Rush University Medical Center, Chicago, Illinois. VIDHI DESAI, MD, and SONGKAI YAN, MS, CSL Behring, King of Prussia, Pennsylvania. GÉRALDINE S. MARO, PhD, Adivo Associates, San Francisco, California.*

AUTHOR CORRESPONDENCE: Songkai Yan, MS, CSL Behring, 1020 First Ave., King of Prussia, PA 19406. Tel.: 610.290.7562; E-mail: Songkai.Yan@csllabehring.com.

DISCLOSURES

This study was funded by CSL Behring. Analyses were conducted by Adivo Associates. Maro is an employee of Adivo Associates. Desai and Yan are employees of CSL Behring. Simpson has received consulting honoraria for participation in advisory boards for CSL Behring, Genentech, Octapharma, and Bioverativ and speakers bureau for Bayer and Novo Nordisk.

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REFERENCES

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1):e1-47.
2. Mannucci PM, Tuddenham EG. The hemophilias—from royal genes to gene therapy. *N Engl J Med*. 2001;344(23):1773-79.
3. Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. *Blood*. 2015;125(13):2038-44.
4. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med*. 2007;357(6):535-44.
5. Lambert T, Benson G, Dolan G, et al. Practical aspects of extended half-life products for the treatment of haemophilia. *Ther Adv Hematol*. 2018;9(9):295-308.
6. Makris M. Prophylaxis in haemophilia should be life-long. *Blood Transfus*. 2012;10(2):165-68.
7. Liew K. Many factor VIII products available in the treatment of hemophilia A: an embarrassment of riches? *J Blood Med*. 2017;8:67-73.
8. Advate (antihemophilic factor [recombinant]) lyophilized powder for reconstitution for intravenous injection. Baxalta U.S. December 2018. Available at: https://www.shirecontent.com/PI/PDFs/ADVATE_USA_ENG.pdf. Accessed January 7, 2020.
9. Iorio A, Krishnan S, Myren KJ, et al. Indirect comparisons of efficacy and weekly factor consumption during continuous prophylaxis with recombinant factor VIII Fc fusion protein and conventional recombinant factor VIII products. *Haemophilia*. 2017;23(3):408-16.
10. Cafuir LA, Kempton CL. Current and emerging factor VIII replacement products for hemophilia A. *Ther Adv Hematol*. 2017;8(10):303-13.
11. Schulte S. Innovative coagulation factors: albumin fusion technology and recombinant single-chain factor VIII. *Thromb Res*. 2013;131(Suppl 2):S2-6.
12. Mahlangu J, Young G, Hermans C, Blanchette V, Berntorp E, Santagostino E. Defining extended half-life rFVIII-A critical review of the evidence. *Haemophilia*. 2018;24(3):348-58.
13. Mahlangu J, Kuliczowski K, Karim FA, et al. Efficacy and safety of rVIII-SingleChain: results of a phase 1/3 multicenter clinical trial in severe hemophilia A. *Blood*. 2016;128(5):630-37.
14. Konkle BA, Stasyshyn O, Chowdary P, et al. Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A. *Blood*. 2015;126(9):1078-85.
15. Mahlangu J, Powell JS, Ragni MV, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood*. 2014;123(3):317-25.
16. Curry N, Albayrak C, Escobar M, et al. Once-weekly prophylaxis with glycoPEGylated recombinant factor VIII (N8-GP) in severe hemophilia A: safety and efficacy results from pathfinder 2 (randomized phase III trial). *Haemophilia*. 2019;25(3):373-81.
17. Reding MT, Ng HJ, Poulsen LH, et al. Safety and efficacy of BAY 94-9027, a prolonged-half-life factor VIII. *J Thromb Haemost*. 2017;15(3):411-19.
18. Dunn A. The long and short of it: using the new factor products. *Hematology Am Soc Hematol Educ Program*. 2015;2015:26-32.
19. Schwartz CE, Powell VE, Su J, Zhang J, Eldar-Lissai A. The impact of extended half-life versus conventional factor product on hemophilia caregiver burden. *Qual Life Res*. 2018;27(5):1335-45.
20. Graf L. Extended half-life factor VIII and factor IX preparations. *Transfus Med Hemother*. 2018;45(2):86-91.
21. Rea C, Dunkerley A, Sorensen B, Rangarajan S. Pharmacokinetics, coagulation factor consumption and clinical efficacy in patients being switched from full-length FVIII treatment to B-domain-deleted r-FVIII and back to full-length FVIII. *Haemophilia*. 2009;15(6):1237-42.
22. Chhabra A, Fogarty PF, Tortella BJ, et al. Real-world analysis of dispensed international units of coagulation factor VIII and resultant expenditures for hemophilia A patients: a comparison between standard half-life and extended half-life products. *Manag Care*. 2018;27(10):39-50.
23. Iorio A, Edginton AN, Blanchette V, et al. Performing and interpreting individual pharmacokinetic profiles in patients with hemophilia A or B: rationale and general considerations. *Res Pract Thromb Haemost*. 2018;2(3):535-48.

24. Klamroth R, Simpson M, von Depka-Prondzinski M, et al. Comparative pharmacokinetics of rVIII-SingleChain and octocog alfa (Advate) in patients with severe haemophilia A. *Haemophilia*. 2016;22(5):730-38.

25. Yu JK, Iorio A, Edginton AN; WAPPS co-investigators. Using pharmacokinetics for tailoring prophylaxis in people with hemophilia switching between clotting factor products: a scoping review. *Res Pract Thromb Haemost*. 2019;3(3):528-41.

26. Poon MC, Lee A. Individualized prophylaxis for optimizing hemophilia care: can we apply this to both developed and developing nations? *Thromb J*. 2016;14(Suppl 1):32.

Comparing Factor Use and Bleed Rates in U.S. Hemophilia A Patients Receiving Prophylaxis with 3 Different Long-Acting Recombinant Factor VIII Products

APPENDIX A Frequency of Prophylaxis Infusions in Patients Using Long-Acting Products

Q2D = dosing every 2 days; Q3D = dosing every 3 days; Q4D = dosing every 4 days; Q5D = dosing every 5 days.

APPENDIX B Frequency of Prophylaxis Infusions in Patients Using Prior FVIII Compared with rVIII-SingleChain