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Comparing Factor Use and Bleed Rates in US Hemophilia A Patients Receiving Prophylaxis With 3 Different Long-Acting Recombinant Factor VIII Products

This AJMC® Clinical Brief provides key information regarding a study by Simpson, et al, the results of which were originally published in the *Journal of Managed Care & Specialty Pharmacy* (doi:10.18553/jmcp.2020.19318). The authors of the original publication are Simpson ML, Desai V, Maro GS, and Yan S. Please consult the full publication for complete study information and author affiliations.

BACKGROUND

An estimated 1 in 10,000 individuals is born with hemophilia A, an uncommon X-linked genetic disorder.¹ Although the majority (70%) of patients inherit hemophilia A, approximately 30% have no family history of this bleeding disorder and acquire it through a spontaneous mutation in the gene that encodes for coagulation factor VIII (FVIII).² Insufficient or total lack of FVIII results in cases of abnormal or uncontrolled bleeding; the severity of these bleeding episodes is associated with the level of residual circulating factors.² Patients with FVIII activity levels less than 1% have severe hemophilia A; the standard of care for these patients is continuous prophylaxis with an FVIII product.^{1,3,4} Prophylaxis is employed to prevent spontaneous bleeding, especially into the joints; it is also associated with a decreased incidence of joint arthropathy and increased overall health and quality of life.^{4,5}

Advances in therapy have greatly changed the treatment landscape for hemophilia A. Nonetheless, although there are several plasma-derived FVIII products and recombinant FVIII (rFVIII) treatments that reduce spontaneous bleeding and joint disease, they are associated with limitations.⁶ For example, the pharmacokinetics of these prophylactic products may require patients to receive several infusions each week, which may influence compliance.^{6,7} Patients may also experience breakthrough bleeding or have difficulties with venous access.^{6,8}

IMPORTANT SAFETY INFORMATION AND INDICATIONS

AFSTYLA®, Antihemophilic Factor (Recombinant), Single Chain, is contraindicated in patients who have had life-threatening hypersensitivity reactions to AFSTYLA or its excipients, or to hamster proteins.

AFSTYLA is for intravenous use only. AFSTYLA can be self-administered or administered by a caregiver with training and approval from a healthcare provider or hemophilia treatment center. Higher and/or more frequent dosing may be needed for patients under 12 years of age.

Hypersensitivity reactions, including anaphylaxis, are possible. Advise patients to immediately report symptoms of a hypersensitivity reaction. If symptoms occur, discontinue AFSTYLA and administer appropriate treatment.

Please see additional Important Safety Information throughout this article and full Prescribing Information for AFSTYLA.

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More recently, rFVIII products that use single chain technology (rVIII-SingleChain; AFSTYLA, CSL Behring), Fc fusion (rFVIII-Fc; Eloctate, Bioverativ), or PEGylation (PEG-rFVIII; Adynovate, Takeda) have been developed. These products offer improved pharmacokinetic profiles and longer half-lives compared with unmodified products.^{1,9} Clinical trials have demonstrated that these products effectively prevent bleeding episodes and enable individualized dosing regimens to achieve FVIII activity levels greater than 1%.¹⁰⁻¹³ Long-acting FVIII products may permit a reduction in dosing frequency, thereby reducing the number of infusions each year, which may reduce treatment burden and increase patient compliance.¹⁴ Compared with patients receiving standard half-life FVIII products, those receiving long-acting FVIII products have been able to reduce their consumption of FVIII units while maintaining similar bleeding rates.⁸ Reduction in consumption may also be associated with a decrease in cost of treatment.¹⁵

METHODS

Simpson et al conducted a retrospective study of patients with hemophilia A in the United States to investigate the real-world use of prophylactic rVIII-SingleChain, rFVIII-Fc, and PEG-rFVIII, and to compare the bleeding rates and factor consumption among those using the 3 products.¹⁵ The investigators also completed a switch analysis in which bleeding rates, dosing frequency, and factor consumption were examined among patients who were switched from prophylaxis therapy with a prior FVIII product to prophylaxis with rVIII-SingleChain.

Data were collected from May 2018 to July 2018 (and for up to 3 years of prior therapy in patients receiving rVIII-SingleChain) using preexisting medical records from 11 hemophilia treatment centers in the United States.¹⁵ Patients were included if they were currently receiving 1 of 3 long-acting FVIII products (rVIII-SingleChain, rFVIII-Fc, or PEG-rFVIII) for a minimum of 8 weeks. To balance the 3 treatment groups, patient selection accounted for age and disease severity when possible.¹⁵ Pediatric patients (those aged <12 years) and adults (aged ≥12 years) were included in the analysis. Disease severity was classified as severe (<1% normal FVIII activity level in the blood), moderate (1% to ≤5%), or mild (>5% to 40%). The primary outcome measures were annualized bleeding rate (ABR) and FVIII consumption.¹⁵ ABR was determined by annualizing the number of bleeding events based on the duration of these episodes. FVIII consumption was normalized by accounting for dose per infusion, number of infusions per week, and patient weight, and reported as international units (IU) per kg per week (IU/kg/week).¹⁵

For the switch analysis, data were collected about the FVIII products patients used before switching to rVIII-SingleChain. The same methods used for the cohort analysis (described above) were applied to compare ABR, dosing frequency, and FVIII consumption among rVIII-SingleChain and prior FVIII products.¹⁵

Analysis of covariance (ANCOVA) models that incorporated age, weight, severity, and consumption as covariates were used to test for statistical significance in ABR among the 3 treatment groups. Differences in FVIII consumption were determined using ANCOVA models that factored in age, weight, and severity of hemophilia A. Differences among the 3 treatment groups for the percentage of patients with no bleeding events were assessed using Fisher's exact test. For the switch analysis, paired *t* tests were used to determine differences in ABR and FVIII consumption between rVIII-SingleChain and prior FVIII products. McNemar's test was employed to assess the statistical significance of differences in the percentage of patients with no bleeding episodes while receiving rVIII-SingleChain compared with prior FVIII products.¹⁵

RESULTS

A total of 120 male patients were included in the analysis. Most patients (90.0%) were adults, and the majority (85.8%) had severe hemophilia A. Most patients in the 3 treatment groups received prophylactic FVIII therapy 2 times a week or less (rVIII-SingleChain, 65.0%; rFVIII-Fc, 70.0%; and PEG-rFVIII, 72.5%). The mean duration of observation was 43 weeks with rVIII-SingleChain and 52 weeks in the rFVIII-Fc and PEG-rFVIII groups.¹⁵

Mean ABRs were comparable among the 3 treatment groups (Table 1).¹⁵ The percentage of patients with no bleeding events was similar among those receiving rVIII-SingleChain (25.0%) and rFVIII-Fc (22.5%) and was slightly lower in those receiving PEG-rFVIII (17.5%); however, these differences were not significant. Among patients with dosing frequencies of 2 or 3 times a week, results were comparable with the overall analysis.¹⁵

Significant differences were observed in mean consumption among the 3 treatment groups (Table 1).¹⁵ Compared with rFVIII-Fc and PEG-rFVIII, mean consumption was lower with rVIII-SingleChain at all dosing frequencies and with 2 weekly doses and 3 weekly doses. In patients receiving rVIII-SingleChain 2 times per week, consumption was approximately two-thirds of the consumption of patients receiving it 3 times per week. Similar results were observed among the 2 dosing regimens for rFVIII-Fc and PEG-rFVIII.¹⁵

IMPORTANT SAFETY INFORMATION AND INDICATIONS (*continued*)

Formation of neutralizing antibodies (inhibitors) has been reported following administration of AFSTYLA; previously untreated patients (PUPs) are at greater risk. If expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures Factor VIII inhibitor concentration.

Monitor plasma FVIII activity using a chromogenic assay or one-stage clotting assay. **If one-stage clotting assay is used, multiply result by a conversion factor of 2 to determine FVIII activity level.**

The most common adverse reactions reported in clinical trials (>0.5%) were dizziness and hypersensitivity.

Compared with the other FVIII products, overall mean consumption was lower with rVIII-SingleChain in patients aged at least 12 years and those aged less than 12 years. Similarly, in patients with severe hemophilia A, mean overall consumption was lower in patients given rVIII-SingleChain compared with those given rFVIII-Fc or PEG-rFVIII.¹⁵

The majority of patients (94.9%) included in the switch analysis were previously using a standard half-life FVIII product, whereas 5.1% were using a long-acting product. Prior to switching therapy, most patients (79.4%) received 3 doses each week; approximately 10.3% received 2 doses each week. After switching therapy to rVIII-SingleChain, about half of patients (53.8%) were able to follow a dosing regimen of 2 times per week. All patients who were receiving prior FVIII therapy once a week (10.3% of the study population) were able to maintain this dosing regimen with rVIII-SingleChain.¹⁵

Overall mean ABR was similar with rVIII-SingleChain compared with prior FVIII therapy; mean ABRs were comparable across dosing frequencies (Table 2).¹⁵ Significantly more patients had no bleeding episodes after switching to rVIII-SingleChain from their prior product (25.6% vs 7.7%, respectively; $P = .0001$). The incidence of spontaneous bleeding events was significantly lower with rVIII-SingleChain than the previous FVIII product (17.9% vs 43.6%; $P = .0321$); however, there was no significant difference in the incidence of traumatic bleeding events (48.7% vs 51.3%; $P = 1.0000$).¹⁵ Across dosing frequencies, switching from prophylaxis with a prior FVIII product to rVIII-SingleChain was associated with a significant reduction in mean consumption (103.3 IU/kg/week vs 91.9 IU/kg/week; $P = .0164$).¹⁵

DISCUSSION

Most patients received 2 or fewer doses of FVIII therapy per week.¹⁵ More frequent dosing was associated with higher FVIII product consumption, and patients receiving 3 infusions per week were generally observed to have a higher ABR than those receiving 2 infusions per week. Although this relationship needs to be explored further,

Table 1. Annualized Bleeding Rates and Consumption Among the 3 FVIII Products¹⁵

	rVIII-SingleChain	rFVIII-Fc	PEG-rFVIII	P
Annualized Bleeding Rate				
Overall	n = 40	n = 40	n = 40	
ABR, mean (SD)	2.6 (2.8)	2.6 (2.8)	3.7 (4.4)	.3814
2x/week dosing	n = 22	n = 14	n = 29	
ABR, mean (SD)	2.3 (2.9)	2.0 (2.9)	3.2 (2.7)	.3401
3x/week	n = 14	n = 9	n = 6	
ABR, mean (SD)	3.2 (3.1)	3.1 (3.0)	7.2 (8.5)	.1926
Consumption (IU/kg/week)				
Overall	n = 40	n = 40	n = 40	
Mean (SD)	91.1 (32.8)	103.6 (41.2)	111.0 (60.4)	.0164
2x/week dosing	n = 22	n = 14	n = 29	
Mean (SD)	81.2 (17.9)	104.4 (22.7)	91.5 (20.9)	<.0001
3x/week dosing	n = 14	n = 9	n = 6	
Mean (SD)	121.9 (24.5)	151.4 (17.8)	128.8 (22.7)	.0433

ABR indicates annualized bleeding rate; FVIII, factor VIII.

Adapted from Simpson et al. *J Manag Care Spec Pharm.* 2020;5:1-9. doi: 10.18553/jmcp.2020.19318.

patients requiring 3 doses each week may have more complicated clinical profiles (ie, higher frequency of bleeding events), and this dosing regimen is thus necessary to manage their bleeding.¹⁵

Using the mean overall consumption for patients aged at least 12 years for each FVIII product, the expected overall mean annual consumption for a 70-kg patient was determined to be 322,140 IU for rVIII-SingleChain, 361,816 IU for rFVIII-Fc, and 373,100 IU for PEG-rFVIII. Assuming wholesale acquisition costs of \$1.65, \$2.23, and \$2.16 per IU (from the Medi-Span Price Rx database), respectively, estimated annual costs were \$531,531, \$806,850, and \$805,896.¹⁵ Although higher rates of consumption were noted in pediatric patients, few of these patients were included in this study and they were not representative of the overall population.¹⁵

Results observed with rVIII-SingleChain in this study are consistent with those from the pivotal clinical trial.^{10,15} Patients switching from prophylaxis with a prior FVIII therapy 3 times per week to rVIII-SingleChain 2 times per week experienced a 23% reduction in consumption. Such changes may result in an estimated 52 fewer infusions each year, which could reduce the burden of disease in many patients.¹⁵ A reduction in infusion frequency may improve tolerability of the regimen and

IMPORTANT SAFETY INFORMATION AND INDICATIONS (continued)

AFSTYLA® (Anti-hemophilic Factor (Recombinant), Single Chain), is indicated in adults and children with hemophilia A (congenital Factor VIII deficiency) for:

- On-demand treatment and control of bleeding episodes
- Routine prophylaxis to reduce frequency of bleeding episodes
- Perioperative management of bleeding

Table 2. Annualized Bleeding Rates in the Switch Analysis¹⁵

	Prior FVIII	rVIII-SingleChain	P
All Patients in Switch Analysis (n = 39)^a			
ABR, mean (SD)	2.9 (2.4)	2.6 (2.9)	.5665
2×/Week Dosing (n = 21)			
ABR, mean (SD)	2.3 (1.4)	2.3 (2.9)	.9366
3×/Week Dosing (n = 14)			
ABR, mean (SD)	3.6 (3.6)	3.2 (3.1)	.7420

ABR indicates annualized bleeding rate; FVIII, factor VIII.

^aFour patients were on once-per-week dosing, 21 patients were on twice-per-week dosing, and 14 patients were on 3-times-per-week dosing.

Adapted from Simpson et al. *J Manag Care Spec Pharm.* 2020;5:1-9. doi:10.18553/jmcp.2020.19318

thereby increase patient adherence.¹⁵ Furthermore, treatment adherence may reduce the incidence of breakthrough bleeding events, which could improve the cost-effectiveness of prophylactic FVIII products.¹⁵ Simpson et al acknowledged that additional studies are needed in larger populations to confirm real-world use and to determine treatment patterns in patients with hemophilia A.¹⁵ Investigators noted that the optimal management of this disorder depends on the patient's lifestyle and the pharmacokinetics of their FVIII product regimen.^{15,16}

Limitations

Limitations of this study include a small sample size and a fairly short duration. Selection bias may exist within this population, and the effect of different patient management strategies could not be measured. As a result, these findings may not be generalizable to the entire population. This analysis may also be limited by incomplete information concerning the location, severity, treatment, and outcomes of bleeding episodes and inability to control for patient activity level and characteristics before initiating the studied products. Compliance was measured to determine consumption; however, calculations for consumption of FVIII products were based on the prescribing information and may not reflect true consumption.¹⁵ The mean duration of assessment was shorter with rVIII-SingleChain than rFVIII-Fc and PEGrFVIII (43 weeks vs 52 weeks); therefore, the percentage of patients with no bleeding events may be somewhat higher with rVIII-SingleChain than would be observed if the duration of treatment were the same.¹⁵

CONCLUSIONS

This is the first real-world data analysis designed to compare the clinical benefits of long-acting FVIII products in patients with hemophilia A.¹⁵ In patients aged at least 12 years, rVIII-SingleChain may offer an 11.0% and 13.7% reduction in overall mean FVIII consumption compared with rFVIII-Fc and PEG-rFVIII, respectively, with comparable ABRs among the 3 products. Long-acting FVIII products often permit fewer infusions per week, which can reduce the burden of this disorder. Among the 3 long-acting FVIII products assessed in this study, rVIII-SingleChain may provide an opportunity for cost savings based on wholesale acquisition price at the time of this analysis.¹⁵ ●

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IMPORTANT SAFETY INFORMATION AND INDICATIONS (continued)

AFSTYLA is not indicated for the treatment of von Willebrand disease.

Please see full prescribing information for AFSTYLA.

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

