Comparison of Real-world Dose and Consumption of Two Extended Half-life Recombinant Factor VIII Products for the Treatment of Hemophilia A in the United States

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Background and objectives

- Prophylactic replacement treatment with recombinant factor VIII (rFVIII) concentrates is the current standard of care for patients with hemophilia A, a recessive congenital bleeding disorder caused by deficient or defective FVIII.[1-3]
- Extended half-life (EHL) rFVIII concentrates have been used for the management of hemophilia and require fewer infusions than standard half-life treatment, but real-world data for the use of EHL rFVIII products are limited.
- This retrospective analysis of US specialty pharmacy data evaluated real-world dosing patterns of two EHL rFVIII products, including weekly dose and infusion frequency, for the prophylactic treatment of patients with hemophilia A without inhibitors:
  - Efmoroctocog alfa: antihemophilic factor (recombinant), Fc fusion protein (rFVIII-Fc) (ELOCTATE®; Bioverativ Therapeutics Inc., Waltham, MA, USA)[4]
  - Rurioctocog alfa pegol: antihemophilic factor (recombinant), PEGylated (ADYNOVATE®, ADYNOVI™; TAK-660, SHP660, BAX 855; Baxalta US Inc., a Takeda company, Lexington, MA, USA).[5]

Methods

Study design and data source

- This study was a retrospective analysis of a US specialty pharmacy database.
- Specialty pharmacy dispensing records were collected between January 1, 2015 and December 31, 2018, in full compliance with Health Insurance Portability and Accountability Act regulations.
- Efmoroctocog alfa[4] and rurioctocog alfa pegol[5] are EHL products, approved for use in adults and children with hemophilia A in the US for:
  - On-demand treatment and control of bleeding episodes
  - Perioperative management of bleeding
  - Routine prophylaxis to reduce frequency of bleeding episodes.
- Treatment regimens for prophylaxis included:
  - Efmoroctocog alfa
    - Patients <6 years of age: 50 IU/kg 2×/week. Dose adjusted based on patient response in range of 25–65 IU/kg at 3- to 5-day intervals; more frequent or higher doses up to 80 IU/kg may be required
    - Patients ≥6 years of age: 50 IU/kg every 4 days. Dose adjusted based on patient response in range of 25–65 IU/kg at 3- to 5-day intervals.
  - Rurioctocog alfa pegol
    - Patients <12 years of age: starting dose of 55 IU/kg 2×/week; maximum 70 IU/kg
    - Patients ≥12 years of age: 40–50 IU/kg 2×/week.

Key patient eligibility criteria

- Patients must have been diagnosed with hemophilia A (International Statistical Classification of Diseases and Related Health Problems [ICD]-9 code 286.0, and ICD-10 code D66).
- Patients with ≥2 consecutive monthly pharmacy dispensing records for efmoroctocog alfa or rurioctocog alfa pegol for prophylaxis and with available weight data were included.
- Patients receiving ≥1 dose/day of prophylaxis or immune tolerance induction therapy were excluded.

Outcome measures

- Outcome measures for this study included:
  - Weekly prophylactic consumption: mean (SD) and median (interquartile range)
  - Dosing frequency: number and percentage of patients with a prophylactic dose recorded once, twice, or 3×/week, or Q3D (every 3 days), Q4D, or Q5D
  - Number and percentage of pharmacy dispensing records with doses ≤50 or >50 IU/kg.
- Outcomes were also analyzed by age.

Statistical analysis

- Descriptive analyses were performed for patient demographic characteristics and clinical conditions.
- Patient characteristics were summarized using mean (SD) for continuous outcomes and counts, and proportions for categorical variables.
- Mean weekly prophylaxis formula:

$$\frac{\text{Dispensed units}}{\text{Number of days between pharmacy dispensing records} \times \text{patient weight}} \times 7$$

  - Dose from the last observed pharmacy dispensing record was excluded, as number of days covered by that record could not be calculated.
- The proportion of patients receiving doses above and below or equal to the prophylactic dose of 50 IU/kg was also calculated.
- Sensitivity analyses were performed:
  - For patients who received efmoroctocog alfa or rurioctocog alfa pegol, ≥12 and <12 years of age
  - Using pharmacy dispensing records from 1 complete year (2017).

Results

Patient baseline characteristics

- 774 patients were included; 506 patients received efmoroctocog alfa and 268 received rurioctocog alfa pegol (**Table 1**).
- Mean (SD) ages of patients who received efmoroctocog alfa and rurioctocog alfa pegol were 24.2 (15.8) and 26.3 (14.9) years, and mean (SD) weights were 68.4 (36.8) and 79.8 (37.7) kg, respectively.
- Proportions of patients <6 years of age (7.5% vs 3.7%) and <12 years of age (24.3% vs 14.5%) were higher with efmoroctocog alfa than with rurioctocog alfa pegol.

Table 1. Baseline characteristics of patients by treatment

Characteristic	Efmoroctocog alfa (Patients, N=506)	Rurioctocog alfa pegol (Patients, N=268)
Age group (as of 2018), n (%)		
0 to <6 years	38 (7.5)	10 (3.7)
6 to <12 years	85 (16.8)	29 (10.8)
12 to <18 years	75 (14.8)	45 (16.8)
≥18 years	267 (52.8)	182 (67.9)
Missing	41 (8.1)	2 (0.8)
Hemophilia A severity,* n (%)		
Mild (>5–30%)†	10 (2.0)	4 (1.5)
Moderate (1–5%)†	26 (5.1)	15 (5.6)
Severe (<1%)†	291 (57.5)	214 (79.9)
Unknown	179 (35.4)	35 (13.1)
Top 4 health care provider states,‡ n (%)		
California	48 (9.5)	26 (9.7)
Florida	102 (20.2)	23 (8.6)
Massachusetts	23 (4.6)	27 (10.1)
Ohio	41 (8.1)	43 (16.0)

*Disease severity as recorded in specialty pharmacy dispensing records.[6]
†Values in parentheses indicate FVIII levels, percentage of normal.
‡Based on data from all 50 states.

Dosing frequency and weekly consumption (2015 to 2018)

- The most frequently reported regimen was 2×/week for both efmoroctocog alfa (45.7%) and rurioctocog alfa pegol (72.4%) (**Table 2**).
- Mean weekly consumption (**Figure 1**) was higher in younger patients for both efmoroctocog alfa and rurioctocog alfa pegol.
- Weekly consumption in patients ≥12 years of age and overall dosing regimen variability tended to be higher for efmoroctocog alfa than for rurioctocog alfa pegol (**Figure 1** and **Table 3**).

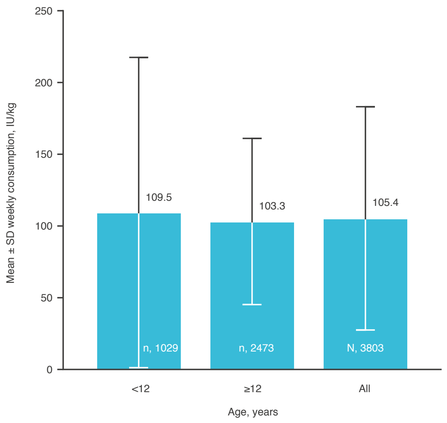
Table 2. Infusion frequency by treatment

Infusion frequency*	2015†	2016	2017	2018	All
Efmoroctocog alfa, n (%)					
1×/week	62 (11.2)	44 (5.2)	74 (5.8)	98 (6.0)	278 (6.5)
2×/week	174 (31.5)	353 (41.7)	608 (47.8)	833 (50.9)	1968 (45.7)
3×/week	37 (6.7)	40 (4.7)	100 (7.9)	147 (9.0)	324 (7.5)
Every 2 days	9 (1.6)	42 (5.0)	66 (5.2)	88 (5.4)	205 (4.8)
Every 3 days	70 (12.7)	94 (11.1)	102 (8.0)	126 (7.7)	392 (9.1)
Every 4 days	173 (31.3)	238 (28.1)	239 (18.8)	238 (14.5)	888 (20.6)
Every 5 days	23 (4.2)	31 (3.7)	55 (4.3)	59 (3.6)	168 (3.9)
Rurioctocog alfa pegol, n (%)					
1×/week	–	16 (6.9)	15 (2.7)	18 (1.9)	49 (2.9)
2×/week	–	156 (67.0)	413 (75.0)	673 (72.2)	1242 (72.4)
3×/week	–	13 (5.6)	44 (8.0)	93 (10.0)	150 (8.7)
Every 2 days	–	2 (0.9)	6 (1.1)	15 (1.6)	23 (1.3)
Every 3 days	–	15 (6.4)	31 (5.6)	48 (5.2)	94 (5.5)
Every 4 days	–	25 (10.7)	32 (5.8)	74 (7.9)	131 (7.6)
Every 5 days	–	6 (2.6)	8 (1.5)	3 (0.3)	17 (1.0)

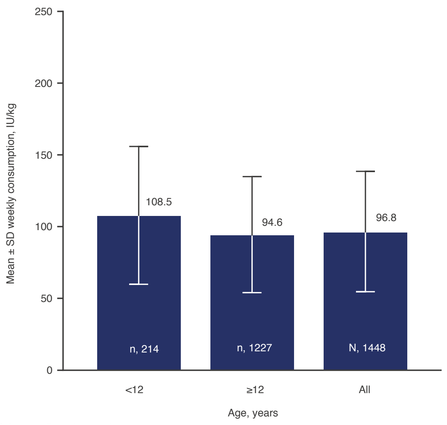
n, number of pharmacy dispensing records.
*Percentages may not total 100%, as some records included alternative regimens.
†Following US approval in June 2014, data for efmoroctocog alfa were available from 2015 to 2018, whereas after approval in November 2015, data for rurioctocog alfa pegol were available from 2016 to 2018.

Figure 1. Weekly consumption by treatment and age (2015 to 2018)

A. Efmoroctocog alfa: patients <12 and ≥12 years of age



B. Rurioctocog alfa pegol: patients <12 and ≥12 years of age



n, number of pharmacy dispensing records.
The N values for both of the "All" columns include records with age missing; 301 missing records for graph A and 7 missing records for graph B.

Sensitivity analyses (2017)

- Sensitivity analyses were performed on data of 1 complete year (2017) after both compounds had been approved for use in the US for ≥1 year.
- For patients ≥12 years of age, mean (SD) weekly consumption and variability were higher in those who received efmoroctocog alfa than in those who received rurioctocog alfa pegol (102.6 [54.0] vs 91.6 [40.0] IU/kg, respectively).
- Mean weekly consumption and variability were higher in patients who received efmoroctocog alfa than in those who received rurioctocog alfa pegol across all cohorts (**Table 3**).

Table 3. Weekly consumption by treatment (sensitivity analysis; 2017 data)

Statistic	Efmoroctocog alfa <12 years of age	Efmoroctocog alfa ≥12 years of age	Efmoroctocog alfa All	Rurioctocog alfa pegol <12 years of age	Rurioctocog alfa pegol ≥12 years of age	Rurioctocog alfa pegol All
Dispensing records, n	278	689	1082	38	413	451
Weekly consumption, IU/kg						
Mean	111.2	102.6	104.5	88.3	91.6	91.3
SD	99.6	54.0	67.5	32.4	40.0	39.4
Median	87.5	92.8	92.2	89.2	86.3	86.4
IQR	65.6–126.6	71.2–113.8	71.1–115.7	56.1–106.6	67.1–108.5	66.6–108.5

IQR, interquartile range.
The n value for efmoroctocog alfa "All" column includes 115 records with age missing.
Sensitivity analyses were performed on data of 1 complete year (2017) after both compounds had been approved for use in the US for ≥1 year.

Limitations

- The specialty pharmacy database does not include all specialty pharmacy providers and therefore may not be representative of all US pharmacies.
- The recording of treatment regimen, infusion frequency, and disease severity may be inconsistent in a pharmacy dispensing records database.
- Treatment selection and clinical response may affect dosing patterns. These factors were not investigated owing to lack of information in the pharmacy dispensing records data.
- Data on clinical outcomes were not available and could not be included in the analysis.
- The number and percentage of patients in the group comprising patients <12 years of age was greater for efmoroctocog alfa than for rurioctocog alfa pegol.

Conclusions

- This retrospective specialty pharmacy database study found that from 2015 to 2018, the proportion of records for 2×/week treatment increased and records for treatment every 4 days decreased in patients who received efmoroctocog alfa.
- Mean weekly consumption was higher and had greater variability in patients who who received efmoroctocog alfa than in those who received rurioctocog alfa pegol, suggesting a potentially higher cost for therapy and less predictable utilization. In part, this may be due to the differences in the prescribing information for the two EHLs.
- Understanding real-world dosing and utilization patterns may help payers understand cost and clinical effectiveness implications for these EHL rFVIII therapies.
- Further research is warranted to investigate the reasons for changes in dosing patterns and the associated clinical outcomes.

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Disclosures:

YW, SS: employees of Shire US Inc., a Takeda company, and Takeda stock owners. TF: employee of Shire US Inc., a Takeda company.

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