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REVIEW ARTICLE

A systematic review evaluating the efficacy and factor consumption of long-acting recombinant factor VIII products for the prophylactic treatment of hemophilia A

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ABSTRACT

Aims: Long-acting (LA) recombinant FVIII (rFVIII) products with extended dosing intervals have been developed for the treatment of hemophilia A; however, no direct head-to-head trial has been conducted to compare the efficacy of these products.

Materials and methods: A systematic literature search was conducted to identify published Phase III clinical trials of prophylactic LA rFVIII treatment in previously treated patients aged ≥12 years, with moderate-to-severe hemophilia A (endogenous FVIII levels ≤2%). Studies that did not meet these criteria, or did not report the included outcomes, were excluded. Bleeding rates and consumption were extracted and summarized; only data for the dosing frequencies indicated in the US product labels (which are similar to those indicated in the European Medicines Agency labels) were included.

Results: Five articles met the inclusion criteria; these studies only included patients with severe hemophilia A. Treatment length, reported outcomes and dose (range: 20–65 IU/kg) varied between studies. Median annualized bleeding rate (ABR) (IQR) reported in the relevant studies was 1.14 (0.00–4.30), rVIII-SingleChain 2 or 3 times weekly; 1.6 (0.0–4.7), rFVIIIFc 2 times weekly followed by every 3–5 days; 1.9 (0.0–5.8), BAX855 2 times weekly; 1.18 (0.00–4.25), N8-GP every 4 days; 1.9 (0.0–5.2) and 4.1 (2.0–10.6), BAY 94-9027 2 times weekly for the cohort who experienced >1 or <1 bleed in the study run-in phase, respectively. Median spontaneous ABR was 0.0 across studies reporting relevant data. Reported consumption was comparable among all LA products.

Limitations: The primary limitation of this systematic review was the variation in study design and not all studies reported all desired outcomes, which limited the quantity of data available.

Conclusions: This systematic review identified pivotal trial data for LA rFVIII products. Real-world evidence is needed to understand how these products perform in clinical practice.

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Introduction

Hemophilia A is an X-linked bleeding disorder characterized by a deficiency or absence of functional coagulation factor VIII (FVIII) resulting in uncontrolled or prolonged bleeding episodes[1]. Bleeding into the joints can cause progressive joint damage and it has been shown that as little as one joint bleed can cause irreversible damage[2]. The primary aim of treatment is to prevent and treat bleeding episodes using replacement FVIII either episodically or by scheduled prophylaxis; many patients with severe hemophilia initiate prophylaxis at an early age[1,3]. Prophylactic replacement FVIII treatment can reduce the risk of joint bleeds, therefore reducing morbidity and chronic disability[4]. The relatively short half-life of traditional FVIII products (8–12 h) means frequent infusions are required for prophylaxis, placing a significant burden on the patient and caregiver[1].

Frequent dosing can be a burden for patients and can negatively affect their quality-of-life, potentially resulting in a lack of treatment adherence that can compromise treatment effectiveness[5,6]. Maintaining FVIII trough levels above 1% is associated with a reduction in bleeding rate and so is often a target for prophylactic therapy. Several recombinant FVIII (rFVIII) products are currently available for the treatment of patients with hemophilia A; however, the pharmacokinetics of standard-acting products are similar to endogenous FVIII, and therefore require infusions 3–4 times weekly to maintain these target trough levels. To overcome this, long-acting (LA) rFVIII products were produced either by increasing half-life compared with full-length rFVIII resulting in improved pharmacokinetic profiles, or by extending the *in vivo* effect of the product thereby enabling an extended dosing interval[7]. A variety of methods have been employed to extend the dosing interval of FVIII products including; single-chain

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technology (rVIII-SingleChain, AFSTYLA[i])[8], Fc-fusion (rFVIIIFc, ELOCTATE[ii])[9], and polyethylene glycol (PEG) conjugation (BAY 94-9027, JIVI[iii]; BAX 855, ADYNOVATE[iv]; N8-GP, ESPEROCT[v])[10–12].

A systematic review and indirect comparison of rFVIIIFc with standard-acting products found reduced bleeding rates, factor consumption, and dosing frequency with rFVIIIFc prophylaxis[13]; however, there have been no similar comparisons for long-acting products. There is a need to understand the differences in efficacy and consumption between available LA rFVIII products in order to enable better clinical treatment decisions for patients with hemophilia A. This manuscript aimed to systematically review the evidence from Phase III clinical trials evaluating the use of LA rFVIII products for prophylaxis in patients with hemophilia A, specifically focusing on bleeding rates and factor consumption.

Methods

In this systematic literature review, we summarized bleeding rates and factor consumption reported in adult and adolescent patients in published Phase III trials for LA rFVIII products available for the prophylactic treatment of hemophilia A.

Search strategy and study selection

A systematic literature search was conducted in both PubMed and EMBASE according to PRISMA guidelines on August 21, 2020. Search terms were designed to select publications according to the patient population and treatment administered; these were then combined into a search string (Table 1). Search terms were limited to articles published in English, with a date range of 1966 (PubMed) or 1968 (EMBASE) to present. Further filters were applied to the EMBASE search to eliminate articles not published in scientific journals and those from the MEDLINE database. All publications retrieved were assessed against predefined inclusion/exclusion criteria to identify Phase III clinical trials of prophylactic LA rFVIII treatment in previously treated patients aged $\geq$12 years, diagnosed with moderate-to-severe hemophilia A (endogenous FVIII levels $\leq$2%) (Table 2). As this review was not a direct head-to-head comparison, various prophylaxis dosing regimens were implemented across products; to limit the potential for bias, for studies with more than one prophylaxis schedule, only data for the dosing frequencies indicated in the US product labels were included. Eligible studies had to report at least one of the following outcome measures; annualized bleeding rate (ABR), spontaneous ABR (AsBR), joint ABR (AjBR), or rFVIII consumption (for rVIII-SingleChain data on file were used). In all studies, patients must have received at least one dose to be included in the efficacy analysis. In order to compare studies more effectively, only Phase III trials were included as these are more likely to have similar sample sizes and study designs due to required regulatory approvals. Initial screening was conducted on the title and abstract of all search results using the pre-defined inclusion/exclusion criteria;

Table 1. Literature search terms.

PubMed	
1	"Factor VIII deficiencies" OR "Factor VIII deficiency" OR "FVIII deficiencies" OR "FVIII deficiency"
2	"Hemophilia A" OR "Haemophilia A"
3	"Factor VIII/administration and dosage"[Mesh] OR "FVIII/administration and dosage"[Mesh] OR "Factor 8/administration and dosage"[Mesh]
4	(("Factor VIII" OR "FVIII" OR "Factor 8") AND ("treatment" OR "drug" OR "therapy" OR "concentrate" OR "recombinant")) OR "rFVIII"
5	"rFVIII-SC" OR "AFSTYLA" OR "rFVIII-SingleChain" OR "CSL627" OR "lonoctocog al*" OR "Advate" OR "octocog al*" OR "rurioctocog al*" OR "rAHF-PFM" OR "Novo8" OR "NovoEight" OR "turoctocog al*" OR "N8" OR "BAY 81-8973" OR "BAY 14-2222" OR "Helixate" OR "Iblias" OR "Kogenate" OR "Kovaltry" OR "rFVIII-FS" OR "Nuwiq" OR "simoctocog al*" OR "rhFVIII" OR "Eloctate" OR "Elocta" OR "efmoroctocog al*" OR "efraloctocog al*" OR "FVIII-Fc" OR "Adynovate" OR "Adynovi" OR "BAX-855" OR "PEG rFVIII" OR "rurioctocog alfa pegol" OR "rurioctocog alpha pegol" OR "BAY 94-9027" OR "damoctocog alfa pegol" OR "damoctocog alpha pegol" OR "rFVIII glycopegylated" OR "PEGylated BDD-rFVIII" OR "N8-GP" OR "turoctocog alfa pegol" OR "turoctocog alpha pegol" OR "rFVIII glycopegylated"
6	"bleed" OR "bleeding" OR "bleedings" OR "bleeds" OR "Blood loss" OR "hemorrhag*" OR "haemorrhag*" OR "ABR" OR "AsBR" OR "jABR" OR "AjBR" OR "annualized bleeding rate" OR "annualized spontaneous bleeding rate" OR "joint annualized bleeding rate" OR "annualised bleeding rate" OR "annualised spontaneous bleeding rate" OR "joint annualised bleeding rate" OR "consumption" OR "trough"
FINAL	(1 OR 2) AND (3 OR 4 OR 5) AND (6)
EMBASE	
1	"Factor VIII deficiencies" OR "Factor VIII deficiency" OR "FVIII deficiencies" OR "FVIII deficiency"
2	"Hemophilia A" OR "Haemophilia A"
3	(("Factor VIII" OR "FVIII" OR "Factor 8") AND ("treatment" OR "drug" OR "therapy" OR "concentrate" OR "recombinant")) OR "rFVIII"
4	"rFVIII-SC" OR "AFSTYLA" OR "rFVIII-SingleChain" OR "CSL627" OR "lonoctocog al*" OR "Advate" OR "octocog al*" OR "rurioctocog al*" OR "rAHF-PFM" OR "Novo8" OR "NovoEight" OR "turoctocog al*" OR "N8" OR "BAY 81-8973" OR "BAY 14-2222" OR "Helixate" OR "Iblias" OR "Kogenate" OR "Kovaltry" OR "rFVIII-FS" OR "Nuwiq" OR "simoctocog al*" OR "rhFVIII" OR "Eloctate" OR "Elocta" OR "efmoroctocog al*" OR "efraloctocog al*" OR "FVIII-Fc" OR "Adynovate" OR "Adynovi" OR "BAX-855" OR "PEG rFVIII" OR "rurioctocog alfa pegol" OR "rurioctocog alpha pegol" OR "BAY 94-9027" OR "damoctocog alfa pegol" OR "damoctocog alpha pegol" OR "rFVIII glycopegylated" OR "PEGylated BDD-rFVIII" OR "N8-GP" OR "turoctocog alfa pegol" OR "turoctocog alpha pegol" OR "rFVIII glycopegylated"
5	"bleed" OR "bleeding" OR "bleedings" OR "bleeds" OR "Blood loss" OR "hemorrhag*" OR "haemorrhag*" OR "ABR" OR "AsBR" OR "jABR" OR "AjBR" OR "annualized bleeding rate" OR "annualized spontaneous bleeding rate" OR "joint annualized bleeding rate" OR "annualised bleeding rate" OR "annualised spontaneous bleeding rate" OR "joint annualised bleeding rate" OR "consumption" OR "trough"
FINAL	(1 OR 2) AND (3 OR 4) AND (5)

Table 2. Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Study type	• Phase III trials • Full original articles	• Review papers • Conference abstracts or proceedings • Opinion pieces • Guidelines • Meta-analyses • Systematic reviews • Editorials • Commentaries • Case reports • Case series • Extension studies • Secondary articles • Retracted articles
Subjects	• Adult human subjects (aged 12–65 years) • Diagnosed with moderate-to-severe hemophilia A (FVIII levels $\leq$ 2%) • Previously treated • Receiving LA rFVIII prophylactically	• Animal models • *In vitro* studies • *Ex vivo* studies • Healthy volunteers • Surgical patients • Patients receiving pdFVIII • Patients receiving standard-acting rFVIII

Abbreviations. LA, long-acting; pdFVIII, plasma-derived FVIII; rFVIII, recombinant FVIII.

those articles passing the initial screening were subjected to a full-text review using the same criteria to determine eligibility.

Data extraction and management

The relevant data from all included publications were collected, with data retrieved according to the desired outcome measures. Data were extracted using a standardized data extraction form and any missing data were requested from corresponding authors.

Results

The literature search identified a total of 8,048 articles, 38 of which passed the initial title and abstract screen (Figure 1). Following a full-text review, five articles met the inclusion criteria. These five studies only included patients with severe or moderately severe hemophilia A, with each study investigating one of the following LA rFVIII products; rVIII-SingleChain (AFSTYLA; CSL Behring)[8], rFVIIIFc (ELOCTATE; Sanofi Genzyme)[9], BAX 855 (ADYNOVATE; Takeda)[12], N8-GP (ESPEROCT; Novo Nordisk)[11], and BAY 94-9027 (JIVI; Bayer)[10] (Table 3).

Study characteristics of the included trials are reported in Table 3. Patient populations were comparable; mean patient age ranged from 28.0–33.1 years and all patients had endogenous FVIII levels of <1%. Median treatment duration ranged from 32.1–299 weeks; however, it should be noted that two of the five studies did not report treatment duration (rVIII-SingleChain and BAX 855). The number of patients in the intent to treat (ITT) population (total number enrolled) in each study were 173 (175) for rVIII-SingleChain[8], 165 (165) for rFVIIIFc[9], 138 (138) for BAX 855[12], 186 (186) for N8-GP[11], and 132 (134) for BAY 94-9027[10]; the proportion of the ITT population treated with prophylaxis during the studies were 84.4%, 86.1%, 87.0%, 94.1%, and 86.4%, respectively. Four studies reported the proportion of patients who received prophylaxis treatment prior to enrollment; 40% for rVIII-SingleChain[8], 53% for rFVIIIFc[9], 72% for BAX 855[12], and 80% for N8-GP[11]. Two studies reported pre-study prophylactic regimens in which the majority of patients were dosing $\geq$3 times weekly[8,9]. Data were included for prophylactic regimens described in the US product label; the dose and regimen varied between studies: rVIII-SingleChain, 20–50 IU/kg 2 or 3 times weekly ($n = 126$)[9]; rFVIIIFc, 25 IU/kg on day 1, 50 IU/kg on day 4, followed by 25–65 IU/kg every 3–5 days ($n = 117$)[10]; BAX 855, 45 ± 5 IU/kg 2 times weekly ($n = 120$)[13]; N8-GP, 50 IU/kg every 4 days ($n = 175$)[12]; BAY 94-9027, 30–40 IU/kg 2 times weekly ($n = 24$, separated into two cohorts)[11] (Table 4). Details of bleeding rates and consumption of the five prophylactic LA rFVIII products are reported in Table 4. Not all studies reported every outcome measure. Median ABR (IQR) reported in the relevant studies ranged from 1.14 (0.00–4.30) for rVIII-SingleChain 2 or 3 times weekly[8] to 4.1 (2.0–10.6) for BAY 94-9027 2 times weekly for patients who experienced >1 bleed in the study run-in phase[10]. Mean ABR was similar across the three studies reporting data; 3.32 for rVIII-SingleChain[8], 3.7 for BAX 855[12], and 3.04 for N8-GP[11]. Median AsBR values were 0 in the four studies which reported it. Mean AsBR was comparable in the two studies that reported data. Three studies reported median AjBR which were also comparable. Mean AjBR was reported in only one study (BAX 855; 1.8)[12].

Reported prophylactic consumption was comparable among all products. Median yearly prophylactic consumption was reported in one study, 4282.9 IU/kg for rVIII-SingleChain[8], and mean yearly consumption was reported in three studies; 4472.5 IU/kg for rVIII-SingleChain[8], 4845 IU/kg for N8-GP[11], 4497.8 IU/kg for BAY 94-9027 for patients who experienced >1 bleed in the study run-in phase[10], and 3341.1 IU/kg for BAY 94-9027 for patients who experienced <1 bleed in the study run-in phase[10]. rFVIIIFc reported mean and median weekly prophylactic consumption (77.9 and 85.4 IU/kg, respectively), which was converted to yearly values to enable comparisons with the other products (4050.8 and 4440.8 IU/kg, respectively)[9]. Median yearly prophylactic consumption for BAX 855 (4546 IU/

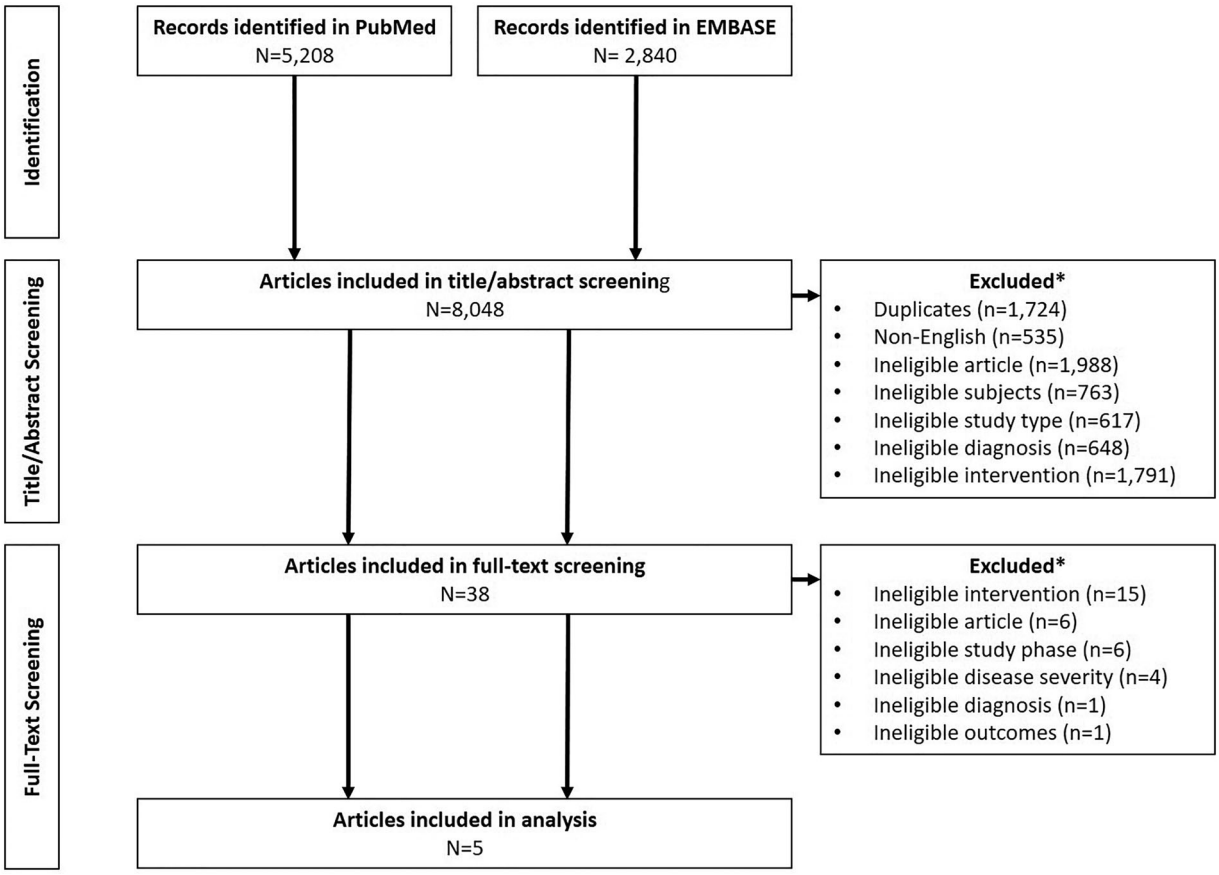

Figure 1. PRISMA diagram detailing the screening process.

Table 3. Study characteristics of included articles.

Study	Product	Design	Phase	Subjects (*n*)	Endogenous FVIII levels	Median treatment duration (weeks)
Mahlangu et al.[8]	rVIII-SingleChain	Open-label, non-randomized	I/III	173 ITT (175 enrolled), 146 prophylaxis	<1%	Not reported
Mahlangu et al.[9]	rFVIIIFc	Open-label, partially randomized	III	165 ITT (165 enrolled), 142 prophylaxis	<1%	(min, max) 32.1 (9, 54)
Konkle et al.[12]	BAX 855	Open-label, non-randomized	II/III	138 ITT (138 enrolled), 120 prophylaxis	<1%	Not reported
Giangrande et al.[11]	N8-GP	Open-label, non-randomized	III	186 ITT (186 enrolled), 175 prophylaxis	<1%	(min, max) Days: 299 (5, 593)
Reding et al.[10]	BAY 94-9027	Partially randomized, open-label	II/III	132 ITT (134 enrolled), 114 prophylaxis	<1%	Mean (SD) Days: 246.7 (41.3)

Abbreviation. ITT, intent-to treat.

kg) was calculated from the reported median dose per infusion (44.6 IU/kg) and the median number of infusions per week (1.96)[12].

Discussion

In view of the lack of head-to-head clinical trials, this review presents data from pivotal trials of different LA rFVIII products. The results of this systematic review demonstrate that currently available LA rFVIII products have comparable efficacy and consumption. While bleeding rates and consumption for rVIII-SingleChain 2 or 3 times weekly ($n = 126$) are data on file, results for these are very close to those published in the pivotal study for all prophylaxis patients ($n = 146$)[8].

Some patients using prophylaxis with LA products during these trials still experienced breakthrough bleeding. ABRs and AsBRs were similar across studies reporting relevant data. Of the labeled dosing regimens indirectly compared in this study, rVIII-SingleChain dosed at 20–50 IU/kg 2 or 3 times weekly and N8-GP dosed at 50 IU/kg every 4 days displayed the lowest ABR compared with the labeled dosing regimens in other studies reporting relevant data. rVIII-SingleChain showed equivalent results in terms of bleeding rates compared with the other products in this review. N8-GP had comparably low mean and median ABR; however, this was the only product to report a median AjBR greater than 0.0 of the three studies which reported it.

The decision to switch to a less frequent dosing regimen should be based on a number of factors including bleeding

Table 4. Details of bleeding rates and consumption in LA rFVIII studies identified by the systematic review.

Product, dose and regimen	Patients (*n*); Age (years), mean (SD)	ABR, median (IQR), mean [SD]	AsBR, median (IQR), mean [SD]	AjBR, median (IQR), mean [SD]	Consumption (IU/kg/year), median	Consumption (IU/kg/year), mean
rVIII-SingleChain; 20–50 IU/kg 2 or 3 × weekly[8]	*n* = 126; 29.7 (11.1)	1.14 (0.00–4.30), 3.32 [5.34]	0.00 (0.00–2.66), 2.33 [5.07]	Not reported	4282.9	4472.5 (SD: 1794.0)
rFVIIIFc; 25 IU/kg on day 1, 50 IU/kg on day 4, followed by 25–65 IU/kg, every 3–5 days[9]	*n* = 117; 29 (12, 65)[§]	1.6 (0.0–4.7), Not reported	0.0 (0.0–2.0), Not reported	0.0 (0.0–1.7),[††] Not reported	4050.8[‡‡]	4440.8[‡‡]
BAX 855; 45 ± 5 IU/kg 2 × weekly[12]	*n* = 120; 28 (12, 58)[§]	1.9 (0.0–5.8), 3.7 [4.7]	0 (0.0–2.2), 2.1 [3.5]	0.0 (0.0–2.0), 1.8 [3.0]	4546[§§]	Not reported
N8-GP; 50 IU/kg every 4 days[11]	*n* = 175; 30.6 (12.5)	1.18 (0.00–4.25), 3.04 [2.45–3.77]**	0.00 (0.00–1.82), Not reported	0.85 (0.00–2.84), Not reported	Not reported	4845
BAY 94-9027; 30–40 IU/kg 2 × weekly[F10]	*n* = 13; 31.4 (11.6)	4.1 (2.0–10.6), Not reported	Not reported	Not reported	Not reported	4497.8
BAY 94-9027; 30–40 IU/kg 2 × weekly[F10]	*n* = 11; 33.1 (11.0)	1.9 (0.0–5.2), Not reported	Not reported	Not reported	Not reported	3341.1

Abbreviations. IQR, interquartile range; IU, international units; SD, standard deviation.
Where data were available for more than one prophylaxis regimen, information is presented for the regimen closest to the initial regimen as recommended in the US product label.
[†]Group who experienced >1 bleed during the study run-in phase so were not eligible for randomization; [‡]group who experienced <1 bleed in the study run-in phase who were eligible for randomization but not randomized as the randomization arms were full; [§]Median (min, max); **Poisson estimate [95% CI]; [††]Spontaneous joint bleeds; [‡‡]Calculated from weekly dose (median 77.9, mean 85.4); [§§]Calculated from median dose per infusion (44.6) and median number of infusions per week (1.96).

phenotype, activity levels, patient lifestyle, and individual pharmacokinetic data. Additionally, patients should be well-controlled on their previous regimen before reducing dosing frequency. Recently, real-world data reported by Simpson et al.[14] and Olivieri et al.[15] showed that patients switching from prophylaxis with prior FVIII products to rVIII-SingleChain could reduce their dosing frequency whilst maintaining or improving efficacy. The reduced dosing frequency and improved pharmacokinetic profile of rVIII-SingleChain (lower clearance, higher mean residence time, and larger area under the curve) compared with standard-acting rFVIII products demonstrates that it shares characteristics with other LA products, making it an effective treatment for hemophilia A whilst reducing consumption, leading to potential cost savings[7,8,14,16].

Of the studies with consumption data available, BAY 94-9027 reported the lowest yearly consumption[10]. Real-world evidence is needed to confirm such data for this recently launched product.

The primary limitation of this systematic review was the variation in study design; the substantial variation in reported treatment dose and prophylaxis regimen potentially weakens any comparisons made between products. As this review was an indirect comparison, various dosing regimens were implemented across the different studies. The dosing regimens selected for comparison in this study were in line with those recommended in the US product label, enabling a comparison of regimens likely to be used in clinical practice. While this is a significant limitation with regards to the strength of the conclusions from this study, it is an expected limitation of this type of comparison. Additionally, in the absence of a head-to-head comparison, which is unlikely to occur in these marketed products, the data provided here provides a comparative guide as to the expected efficacy and consumption of these products, as recommended in the product label. The comparison between products was also limited in that not all studies reported all desired outcomes. In addition, this review is limited by the small number of studies identified, with only one study found for each of the LA rFVIII products; this limited the quantity of data available for comparison. The rarity of hemophilia A and the low number of patients worldwide, eligible and willing to participate in clinical trials, limits the amount of available data; it may be valuable to carry out a similar review with expanded criteria, for example, including real-world data. As is common among systematic reviews and literature searches, another limitation is the potential for publication bias, although the methods described in this study were selected to reduce the impact of such bias.

Conclusion

This systematic review identified pivotal trial data for LA rFVIII products. These data showed that LA rFVIII products can provide adequate protection from bleeding with similar consumption in patients with hemophilia A. Given the lack of direct head-to-head trials of rFVIII products, this review provided a summary of the efficacy and consumption data

of different LA rFVIII products from relevant pivotal trials. Further comparative real-world data are needed to assess how these products perform in clinical practice.

Notes

i. AFSTYLA is a registered trademark of CSL Behring, Germany.
ii. ELOCTATE is a registered trademark of Sanofi Genzyme, USA.
iii. JIVI is a registered trademark of Bayer, USA.
iv. ADYNOVATE is a registered trademark of Takeda, Japan.
v. ESPEROCT is a registered trademark of Novo Nordisk, USA.

Transparency

Declaration of funding

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Declaration of financial/other interests

LG: consultancy for CSL Behring, Novo Nordisk, Octapharma, Roche and SOBI; SY: employee of CSL Behring; MCS: no conflicts of interest; VB: consultancy for Bayer, Bioverativ/Sanofi Genzyme, CSL Behring, Novartis and Shire.

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Previous presentations

The results of this literature search were presented as a poster at ISTH 2019 and EAHAD 2020.

References

[1] Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. Haemophilia. 2013;19(1):e1.
[2] van Vulpen LFD, Holstein K, Martinoli C. Joint disease in haemophilia: pathophysiology, pain and imaging. Haemophilia. 2018; 24(Suppl 6):44–49.
[3] 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):535–544.
[4] Fischer K, van der Bom JG, Mauser-Bunschoten EP, et al. The effects of postponing prophylactic treatment on long-term outcome in patients with severe hemophilia. Blood. 2002;99(7): 2337–2341.
[5] Wiley RE, Khoury CP, Snihur AWK, et al. From the voices of people with haemophilia A and their caregivers: challenges with current treatment, their impact on quality of life and desired improvements in future therapies. Haemophilia. 2019;25(3): 433–440.
[6] Thornburg CD, Duncan NA. Treatment adherence in hemophilia. Patient Prefer Adherence. 2017;11:1677–1686.
[7] Escobar M, Santagostino E, Mancuso ME, et al. Switching patients in the age of long-acting recombinant products? Expert Rev Hematol. 2019;12(sup1):1–13.
[8] Mahlangu J, Kuliczkowski 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):630–637.
[9] 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):317–325.
[10] 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):411–419.
[11] Giangrande P, Andreeva T, Chowdary P, et al. Clinical evaluation of glycoPEGylated recombinant FVIII: efficacy and safety in severe haemophilia A. Thromb Haemost. 2017;117(2):252–261.
[12] 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):1078–1085.
[13] 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):408–416.
[14] Simpson ML, Desai V, Maro GS, et al. Comparing factor use and bleed rates in U.S. hemophilia A patients receiving prophylaxis with 3 different long-acting recombinant factor VIII products. J Manag Care Spec Pharm. 2020;5:1–9.
[15] Olivieri M, Sommerer P, Maro G, et al. Assessing prophylactic use and clinical outcomes in hemophilia A patients treated with rVIII-SingleChain and other common rFVIII products in Germany. Eur J Haematol. 2020;104(4):310–317.
[16] 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):730–738.