







ORIGINAL ARTICLE

Clinical haemophilia

Patients' and parents' satisfaction with, and preference for, haemophilia A treatments: a cross-sectional, multicentre, observational study

Young Shil Park¹  | Tai Ju Hwang² | Goon Jae Cho³ | Soon Ki Kim⁴  | Sang Kyu Park⁵ | Ji Yoon Kim^{6,7} | Hee Jo Baek⁸  | Young-Joo Kim⁹  | Ho-Jin Lee⁹ | Ji-Soo Shin⁹ | Chung-Mo Nam¹⁰  | Jiyu Sun¹⁰ | Ki Young Yoo¹¹ 

¹Department of Pediatrics, Kyung Hee University Hospital at Gangdong, Seoul, South Korea

²Korea Hemophilia Foundation Gwangju Clinic, Gwang-Ju, South Korea

³Korea Hemophilia Foundation Busan Clinic, Busan, South Korea

⁴Department of Pediatrics, Inha University Hospital, Incheon, South Korea

⁵Department of Pediatrics, Ulsan University Hospital, Ulsan, South Korea

⁶Department of Pediatrics, Kyungpook National University Hospital, Daegu, South Korea

⁷Department of Pediatric Hematology and Oncology, Kyungpook National University Chilgok Hospital, Daegu, South Korea

⁸Department of Pediatrics, Chonnam National University Hwasun Hospital, Chonnam National University Medical School, Gwangju, South Korea

⁹Medical Department, Pfizer Pharmaceuticals Korea Ltd, Seoul, South Korea

¹⁰Department of Biostatistics and Computing, Yonsei University, Seoul, South Korea

¹¹Korea Hemophilia Foundation Clinic (KHF Clinic, Seoul, South Korea)

Correspondence

Ki Young Yoo, Department of Pediatrics, Korea Hemophilia Foundation, 70, Saimdang-ro, Seocho-ku, Seoul, 06641, Korea.
Email: gowho@hotmail.com

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Pfizer Pharmaceuticals Korea Ltd

ABSTRACT

Introduction: Reports on patients' satisfaction and preferred characteristics for treatments would be worthwhile when choosing an optimal treatment reflecting patients' perspectives.

Aim: To identify the characteristics and treatment patterns of patients with haemophilia A, or their caregivers, in Korea and explore patient preferences and satisfaction with their treatment.

Methods: This cross-sectional, multicentre, observational study was conducted from April 2018 to September 2019 at six nationwide hospitals and three Korea Hemophilia Foundation clinics. Patients aged ≥ 16 years, or legal caregivers of paediatric patients, who had used factor VIII (FVIII) concentrates for ≥ 1 month were enrolled. Satisfaction with treatment was measured using the Treatment Satisfaction Questionnaire for Medication (TSQM); preference was evaluated using discrete choice experiment (DCE), with 10 series of two hypothetical treatment options created from *D-efficient* block design, which varied across five attributes.

Results: Overall, 505 patients (mean age 31 years) were enrolled in the study. Patients had received FVIII concentrate for an average of 102.9 months (prophylaxis: 53.5%; on-demand: 22.2%). Mean TSQM scores were 64.6 (effectiveness domain), 97.9 (side effects), 57.1 (convenience) and 66.8 (global satisfaction). The number of vials per injection, and the frequency of drug administration, was significantly associated with treatment satisfaction. According to DCE, simpler treatment options were preferred by patients/caregivers.

Conclusion: The lowest satisfaction levels were shown in the treatment convenience domain. Patients/parents preferred simpler and easier treatment characteristics. In an attempt to enhance the overall satisfaction of patients and caregivers with treatment, consideration of more convenient characteristics is required in future decisions regarding treatment selection.

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KEYWORDS

factor VIII, haemophilia, preference, satisfaction, treatment

1 | INTRODUCTION

Haemophilia is usually an inherited bleeding disorder caused by a lack or decrease in coagulation factors which can result in various types of bleeding because the blood does not clot properly.¹ Coagulation factor VIII (FVIII) is missing or defective in haemophilia A.

In haemophilia patients, bleeding can occur in joints, muscles and major organs. These bleeding and other complications often lead to a decrease in patients' overall quality of life (QoL).² In accordance with guidelines for the management of haemophilia published by World Federation of Hemophilia (WFH), the primary aim of haemophilia care is to prevent and treat bleeding with the deficient clotting factor.³

Although it is important to administer the correct treatment for haemophilia patients to prevent and treat bleeding, the main factor affecting adherence to treatment includes high perceived burden of treatment.⁴ Furthermore, satisfaction with treatment decreases as patients experience difficulties due to the time-consuming nature of treatment and a lack of awareness of treatment effects.⁵ Because haemophilia treatment is usually via self-injection and continues for the lifetime of individuals, factors which may interfere with, or negatively affect, patient adherence and compliance should be considered in order to decrease complications of haemophilia and improve QoL for these patients.

It is important to choose appropriate treatment options which can minimize the impact of these factors and improve treatment adherence and satisfaction for haemophilia patients. In this regard, to achieve the best treatment outcomes, it is necessary to investigate what treatment options are preferred by haemophilia patients and/or caregivers because they usually inject directly.

This study aimed to identify the characteristics and treatment patterns of patients with haemophilia A in Korea and explore patient preferences and satisfaction with their treatment. The study is expected to increase the understanding of haemophilia A patients in Korea and to establish a basis in clinical practice for physicians' decision-making for treating patients from the perspective of patients.

2 | MATERIALS AND METHODS

2.1 | Study design

This cross-sectional, nationwide, multicentre, observational study was conducted from April 2018 to September 2019 at six nationwide hospitals and three Korea Hemophilia Foundation (KHF) clinics, which are representative of haemophilia treatment centres in Korea.

2.2 | Patients' eligibility

Patients (i) aged ≥ 16 years, (ii) diagnosed with haemophilia A with or without an inhibitor, (iii) treated with FVIII concentrate by self-injection

and (iv) treated with their current FVIII treatment pattern (prophylaxis and/or on-demand therapy) for at least 1 month were enrolled in this study. Further, a parent or legal representative, who injects FVIII concentrates to a haemophilia A patient aged 18 years and under and who meets eligibility criteria (ii)–(iv) above, was also enrolled in this study. In cases where a parent or legal representative had two or more children with haemophilia A and administers FVIII to the children, only data for the 1st child were collected for this study.

Patients treated with FVIII concentrate in an admission facility, or those who were injected by a non-legal representative, or treated with bypassing agent other than FVIII concentrate, were excluded from this study.

Prior to enrolment and study participation, all patients and parents read and signed the written consent forms.

2.3 | Sample size

Based on the descriptive observational study design, no specific statistical method for sample size estimation was required. When we designed this study, the total number of haemophilia A patients registered with the KHF in 2016 was 1683.⁶ Of those, around 50% were registered at the participating hospitals of this study. As we assumed the patients' refusal rate for study participation would be 30%, we expected that around 580 patients would be eligible for the study.

2.4 | Data collection

Prior to study commencement, the Institutional Review Board (IRB) of each participating centre provided approval for the study. Regarding ethics approval for the three KHF clinics, the Korean Public IRB approved the conduct of the study since no internal IRB was established for the KHF clinics.

For data collection, both medical chart review and patient survey were used. Data on patients' demographics, clinical characteristics, treatment patterns and bleeding episodes for the latest month during treatment with current FVIII concentrates were collected through medical chart review. Patients' and parents' satisfaction with treatment was measured using the Treatment Satisfaction Questionnaire for Medication (TSQM; ver 1.4).⁷ TSQM is a validated and self-reported questionnaire, containing 14 questions, and is divided into the following four domains: effectiveness, side effects, convenience and global satisfaction. Using the provided scoring equation, total scores in each domain were calculated, rated from 0 to 100. A higher score indicates better satisfaction in the domain.

Depending on the device used to reconstitute FVIII, preparation may involve, for example, two vials, a double-sided needle to transfer the diluent into the FVIII vial, or a syringe into which the reconstituted FVIII product is transferred.⁸ Regarding patients' and parents'

preference for treatment, we performed a discrete choice experiment (DCE) with 10 series of two hypothetical treatment options created from a *D-efficient* block design, which varied across the following five attributes: (i) reconstitution device (RCD) types: prefilled dual-chamber (PDC) syringe, prefilled syringe connected with a vial and two connected vials; (ii) frequency of drug administration: twice or more a week, once a week and twice or less a month; (iii) number of vials per injection: 1 vial, 2 vials and 3 vials; (iv) diluent volume per injection: 5 ml or less, 6–10 ml and 11–20 ml; and (v) time required for reconstitution: under 1 min, 1–2 min and more than 2 min.

2.5 | Statistical analysis

Descriptive data analysis was performed to analyse the variables of demographics, clinical characteristics, treatments, bleeding events and TSQM. We presented continuous data as basic statistics such as number of observations, means and standard deviations, and categorical variables as frequency and percentage (%).

To compare TSQM scores according to demographic and clinical variables, Student's *t* test and Mann-Whitney *U* test were utilized, depending on whether the variable follows a normal distribution. Subsequently, multiple linear regression in each domain was performed to determine the clinical factors associated with TSQM scores using all collected variables.

For preference, count analysis was carried out based on the frequency of chosen and not chosen options. The chosen option was counted as 'best', and the not chosen option was counted as 'worst'. Positive BW (Best-Worst) score indicates predominantly 'best' choice. A conditional logistic regression model was used to estimate the relative importance of the five attributes and to show part-worth utility, which indicates more preference with higher utility. We also derived the mean relative importance of each attribute by calculating the mean maximum range between the part-worth utility associated with the favoured and unfavoured level of the attribute from 1000 bootstrap samples. To compute the 95% confidence interval (CI) of the mean relative importance, we obtained values for the 2.5 and 97.5 percentile of their distribution based on bootstrap replications.

All final significance levels reported were two-tailed, and statistical significance was estimated at $p \leq .05$. Statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute).

3 | RESULTS

A total of 505 patients were enrolled in this study (mean age 31.5 years, mean duration of haemophilia 278.1 months). Of this total, 87.7% of patients had severe haemophilia, $\leq 1\%$ had an inhibitor or central venous catheter, and 69.9% had arthropathy (Table 1). Inhibitor patients who were low responders had injected high-dose FVIII concentrate. The actual number of enrolments during the study period was close to our estimation as 505 patients and parents, which represents approximately 30% of the total registered number of haemophilia A patients, finally participated in the study.

TABLE 1 Demographics and clinical characteristics

Characteristics	N = 505
Age (years), mean (SD)	31.5 (14.2)
Sex, n (%)	
Male	503 (99.6)
Female	2 (0.4)
BMI (kg/m ²), mean (SD)	24 (4.3)
Disease duration (months), mean (SD)	278.1 (101.9)
Severity, n (%)	
Severe	443 (87.7)
Moderate	54 (10.7)
Mild	8 (1.6)
Inhibitor, n (%)	
Yes	3 (0.6)
Transient	3 (100)
Persistent	0 (0.0)
No	502 (99.4)
Central venous catheter, n (%)	
Yes	5 (1.0)
No	499 (98.8)
Unknown	1 (0.2)
Arthropathy, n (%)	
Yes	353 (69.9)
No	139 (27.5)
Unknown	13 (2.6)

Abbreviations: BMI, body mass index; SD, standard deviation.

3.1 | Treatment patterns and bleeding events

Patients had been treated with FVIII concentrate for an average of 102.9 months. Overall, 53.5% of patients received prophylaxis and 22.2% were treated on demand. Most patients (79.0%) used two connected vials while only 6.3% used a PDC syringe. The majority of patients (91.9%) used ≤ 5 ml of diluent solution, 72.9% of patients administered treatment twice or more a week, and 49.1% and 32.7% of patients used 2 vials or 3 vials per injection, respectively (Table 2).

Bleeding was experienced by 264 (52.3%) patients of the total patient population during the latest month on the current treatment, with an average 3.2 bleeding episodes per patient. Of the total number of patients, 190 (37.6%), 73 (14.5%), and 4 (0.8%) patients experienced mild, moderate or severe bleeding, respectively. An average of 2.8 mild bleeding events, 4.2 moderate bleeding events and 1 severe bleeding event occurred (Table 3).

3.2 | Treatment satisfaction and its associated factors

Mean TSQM scores were 64.6 for effectiveness, 97.9 for side effects, 57.1 for convenience and 66.8 for global satisfaction (Figure 1). In univariate analyses, age, disease duration, disease severity, inhibitor,



TABLE 2 Current treatment pattern

	(N = 505)
Duration of treatment (months), mean (SD)	102.9 (59.8)
Treatment methods, n (%)	
Prophylaxis	270 (53.5)
On demand	112 (22.2)
Both prophylaxis and on demand	123 (24.3)
Reconstitution device type, n (%)	
PDC syringe	32 (6.3)
Prefilled syringe connected with a vial	74 (14.7)
Two connected vials	399 (79.0)
Diluent volume, n (%)	
≤5 ml	464 (91.9)
6–10 ml	14 (2.8)
11–20 ml	1 (0.2)
Others	26 (5.1)
Number of vials per injection, n (%)	
1	45 (8.9)
2	248 (49.1)
3	165 (32.7)
≥4	47 (9.3)
Frequency of drug administration, n (%)	
≥Twice a week	368 (72.9)
Once a week	80 (15.8)
≤Twice a month	57 (11.3)
Dose of factor VIII, IU, mean (SD)	1937.3 (535.4)

Abbreviations: IU, international unit; PDC, prefilled dual-chamber syringe; SD, standard deviation.

RCD type, frequency of drug administration and number of bleeding events affected treatment satisfaction of patients and parents (Appendix 1).

After adjusting factors, the number of vials per injection and the frequency of drug administration were significantly associated with treatment satisfaction ($p < .05$). More frequent administration of drug lowered treatment satisfaction in the effectiveness and global satisfaction domains. Patients consuming four or more vials per injection reported lower satisfaction in the global domain compared with patients consuming one vial per injection (Figure 2). For the side effect domain, multiple linear regression was not considered in this analysis because most of the patients in this study did not experience side effects, meaning that side effect scores were 100 in most of the patients.

3.3 | Preferences for the characteristics of treatments

Based on BW score, administration two times/month or less (0.4), PDC (0.2), <1 min for reconstitution (0.1), administration two times/week or more (−0.4), 2 vials/administration (−0.2) and two connected

TABLE 3 Bleeding events (N = 505)

Total, n (%)	
No	241 (47.7)
Yes	264 (52.3)
Number of bleeding event, mean (SD)	3.2 (3.1)
Mild bleeding	
No	315 (62.4)
Yes	190 (37.6)
Number of mild bleeding, mean (SD)	2.8 (2.1)
Moderate bleeding	
No	432 (85.5)
Yes	73 (14.5)
Number of moderate bleeding, mean (SD)	4.2 (4.8)
Severe bleeding	
No	501 (99.2)
Yes	4 (0.8)
Number of severe bleeding, mean (SD)	1.00

Abbreviation: SD, standard deviation

vials (−0.1) all heavily influenced choices. Those choices, representing more simpler treatment options, were preferred whereas options which were manifold in manipulation of the drug were mostly rejected (Table 4). The highest mean relative importance was shown in frequency of drug administration, for which the levels were associated with the largest differences between the lowest and highest β -weights, followed by RCD type (Table 5 and Figure 3). With regard to preference weights for each level within each attribute, less frequent drug administration and PDC syringe in the RCD type presented the highest part-worth utility (Figure 3).

4 | DISCUSSION

As treatment options for haemophilia A patients have expanded in recent years, complex decisions regarding which treatments to initiate and continue have been increasingly demanded. When making treatment decisions, the perspectives of patients and caregivers regarding treatments are absolutely essential because patients with haemophilia A need to administer the missing coagulation factor over their lifetime. This study aimed to describe treatment patterns of haemophilia A patients or caregivers in Korea and investigate their satisfaction and preferences for treatment characteristics.

According to the 2018 annual report published by the KHF, there are 1721 patients registered in Korea with haemophilia A and 73% have a severe form of the disease.⁹ Patients who were capable of self-injection account for 70% of the total 1721 patients with haemophilia A who are registered with the KHF. In the same year, we recruited a total of 505 patients from nine representative hospitals/clinics treating haemophilia in Korea. Compared with the 2018 KHF report, the current study included a higher proportion of patients with severe haemophilia A (72.6% vs 87.7%) and with arthropathy

FIGURE 1 Treatment satisfaction: TSQM scores in each domain [Colour figure can be viewed at wileyonlinelibrary.com]

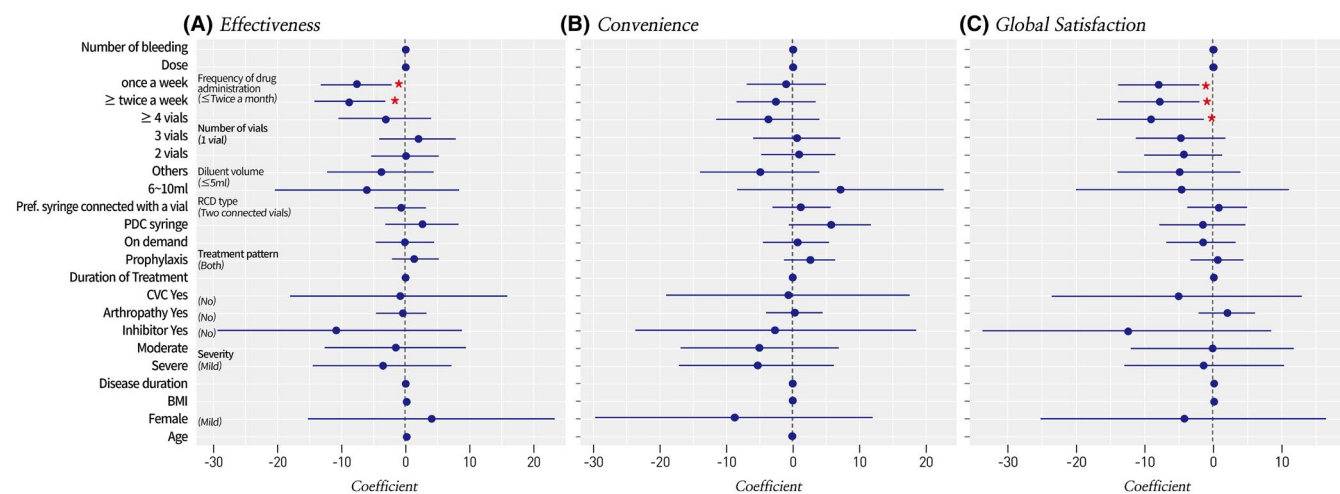
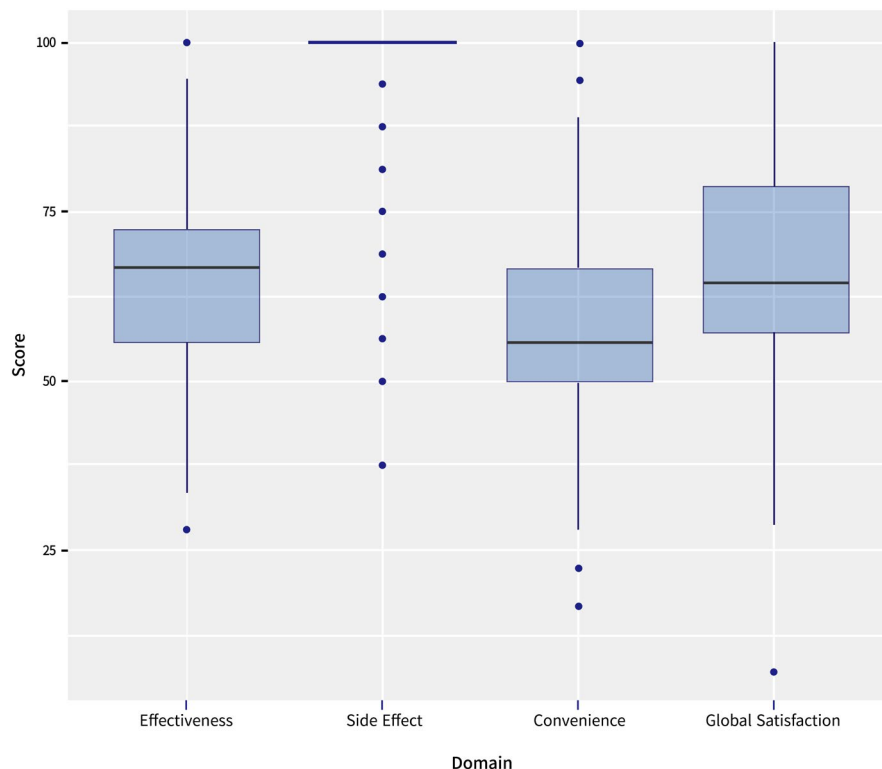


FIGURE 2 Factors associated with treatment satisfaction: TSQM. Footnote: * $p < .05$. Abbreviations: Pref., prefilled; RCD, reconstitution device; PDC, prefilled dual chamber; CVC, central venous catheter; BMI, body mass index [Colour figure can be viewed at wileyonlinelibrary.com]

(57.8% vs 69.9%), but a lower proportion of patients with transient inhibitors (1.6% vs 0.6%).⁹

Haemophilia A patients are treated with FVIII concentrate as prophylaxis or on-demand therapy. Better outcomes and cost-effectiveness are evident with prophylaxis compared with on-demand therapy, as proven in numerous studies.¹⁰⁻¹⁴ However, only around half of patients were treated prophylactically in this study and around 70% of patients were prescribed to administer treatment two or more times per week. As the Korean government allows physicians to prescribe all launched products in Korea and patient preference could be considered in the treatment prescription driven by

physicians through discussion, the following reasons would contribute to those results; on the one hand, this may be due to restrictions in the reimbursement guideline of the National Health Insurance Service; on the other hand, it may reflect patients' own volition for on-demand therapy. The Korean reimbursement guideline restricts coverage up to 20-25 IU/kg per injection, but to a maximum of 30 IU/kg in cases of moderate and severe bleeding. The guideline allows 10 times injections per prescription (12 times for severe patients), meaning 10 times (12 times for severe patients) per 4 weeks in total. In case of bleeding after 10 times injections per 4 weeks (12 times for severe patients), prescriptions for two times injections



Medication attributes and levels	Chosen		Not chosen		BW Score (Difference of %)
	Frequency	%	Frequency	%	
Reconstitution device type					
PDC syringe	2327	46.1	1206	23.9	0.2
Prefilled syringe connected with a vial	1268	25.1	1759	34.9	-0.1
Two connected vials	1452	28.8	2082	41.2	-0.1
Frequency of drug administration					
≥ Twice a week	711	14.1	2821	55.9	-0.4
Once a week	1577	31.2	1450	28.7	0
≤ Twice a month	2759	54.7	776	15.4	0.3
Number of vials per injection					
3	1689	33.5	1338	26.5	0.1
2	1279	25.3	2256	44.7	-0.2
1	2079	41.2	1453	28.8	0.1
Diluent volume					
<5 ml	1520	30.1	1507	29.8	0
6-10 ml	1926	38.2	1608	31.9	0.1
11-20 ml	1601	31.7	1932	38.3	-0.1
Time required for reconstitution					
<1 min	2074	41.1	1460	28.9	0.1
1 ≤ min <2	1442	28.6	1584	31.4	0
≥2 min	1531	30.3	2003	39.7	-0.1

Abbreviation: PDC, prefilled dual-chamber syringe.

are allowable for reimbursement.¹⁵ The doses correspond to only low to intermediate prophylaxis in WFH guidelines and do not fully meet the dose recommended in the drug label for prophylactic use of FVIII.^{3,16}

To maintain the proven outcomes of treatment, drug adherence plays a major role. Drug adherence in haemophilia patients has been reported to vary widely (35-95%) in previous studies.¹⁷ As part of enhancing the efficiency and adherence of treatments, more convenient types of reconstitution devices have been introduced. A PDC syringe is one of the devices launched with the specific aim of rendering treatment less burdensome; PDC syringes were introduced in Korea in 2015. However, only a limited number of patients ($N = 32$, 6.3%) were prescribed FVIII concentrate in a PDC syringe in this study, which reflects the fact that patients have been skilled for a long time with the device type that they have been using.

Regarding patients' or caregivers' satisfaction with treatment, considerably higher satisfaction was reported in three of the TSQM domains, effectiveness (mean score 65), side effects (98) and global satisfaction (67), compared with treatment satisfaction reported in previous studies on other chronic diseases in Korea.^{18,19} In previous studies using the TSQM, patients with postmenopausal osteoarthritis (PMO) reported treatment satisfaction as 56 in effectiveness, 64 in side effects and 54 in the global domain, and patients with atrial fibrillation (AF) treated with

TABLE 4 Results of count analysis ($N = 505$)

TABLE 5 Mean relative importance of attributes and 95% CI

	Relative importance of attributes (%)	Upper CI	Lower CI
Reconstitution device type	20.6	17.2	24.1
Frequency of drug administration	57.8	53.9	62.1
Number of vials per injection	13.0	8.0	17.1
Diluent volume	1.0	0.04	2.9
Time required for reconstitution	7.5	5.6	9.3

Abbreviation: CI, confidence interval.

vitamin K scored their treatment satisfaction as 58, 58 and 56 for the TSQM domains of effectiveness, side effects and global satisfaction, respectively.^{18,19} Satisfaction with treatment convenience was reported the lowest (mean score 57) among all TSQM domains in this study which is similar to that reported by patients with AF treated with vitamin K (58), and slightly lower than the mean score (63) reported by patients with PMO.^{18,19} Surprisingly, satisfaction with treatment convenience in our study was remarkably lower than that reported in patients with haemophilia using PDC syringes in Italy.²⁰

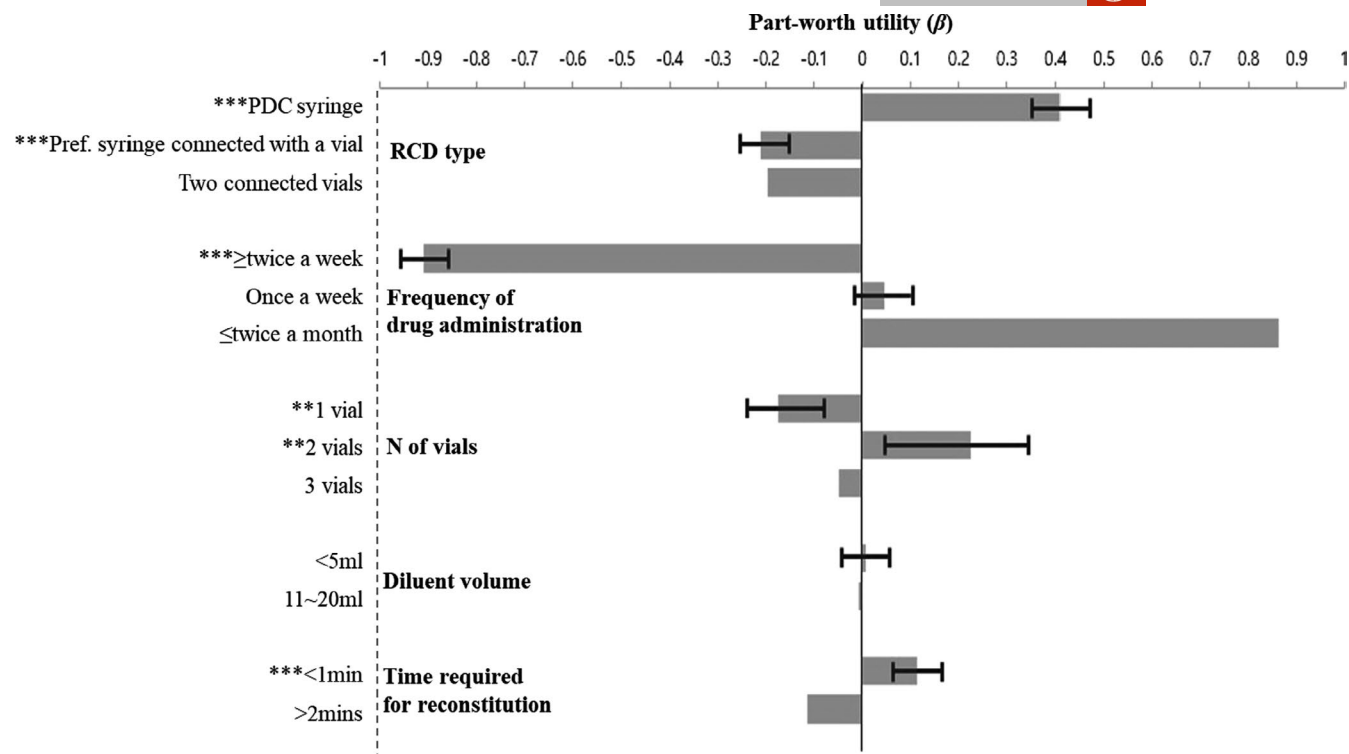


FIGURE 3 Choice-Based conjoint utilities and importance summary of medication attribution. Footnote: *** $p < .001$, ** $p < .01$. No p -values or CIs (lower/upper bound) computed for reference levels from effect coding. Reference levels in effect coding are indicated by (-). Attribute levels' positive β -weights reflect biases toward "best" choices and negative β -weights reflect biases toward "worst" choices. Abbreviations: PDC, prefilled dual chamber; Pref., prefilled; RCD, reconstitution device; N, number

Treatment satisfaction was negatively associated with more frequent administration of drug and consuming four or more vials per injection compared with consuming one vial per injection, which may derive from the fact that patients who remain in an uncontrolled condition are usually prescribed treatment at a higher dose and frequency. A previous systematic review determined that perceived health improvement was positively related to better satisfaction, whereas experience of side effects resulted in a negative impact on satisfaction.²¹

Haemophilia A patients and caregivers in this study showed their preference for simpler and more convenient treatment characteristics, such as lower frequency of drug administration and easier RCD types, which is consistent with the results of previous studies. In an international study conducted in Australia, Canada and the United States (US), frequency of drug administration was the most important attribute related to the preference of haemophilia patients.²² In a US study, lower frequency of drug administration was preferred by haemophilia patients.²³ Frequency of injections and participation in physical activity were important attributes for patients/caregivers in a large Swedish cohort.²⁴ In addition, preferences for PDC syringes, compared with other RCD types, were reported in several prior studies.^{8,25}

4.1 | Limitations

Circumspection is required in the generalization and interpretation of the results since there are several limitations of this study: The

study could only include patients treated with FVIII administered intravenously, since treatments administered subcutaneously, such as emicizumab, a new treatment option for haemophilia A which has been reported to enhance patients' adherence to treatment was not launched in Korea at the time of patient enrolment in this study^{26,27}; based on the cross-sectional design of this study design, no causal relationship between factors and treatment satisfaction was identified; as a self-reported questionnaire was used, the understanding of each question could have varied among individuals; attributes used in discrete choice sets did not include the efficacy and safety profile of drugs.

Notwithstanding these limitations, this study has notable strengths. Although haemophilia is a relatively rare disease, the study involved a meaningful sample size of patients from several hospitals/clinics located regionally throughout Korea. To the best of our knowledge, this is the first ever study to identify treatment satisfaction and preference among haemophilia A patients and caregivers in Korea. As the perceptions of patients and caregivers to treatments can vary depending on the availability of treatment options and treatment patterns within a country, this study provides an in-depth understanding of the personal view of haemophilia A patients or caregivers regarding their treatments in Korea. Further, this study used a validated measurement tool for satisfaction and a rigorous DCE method, both of which have been used widely, so that the results of this study will serve as a source of comparison with results from future studies on the same subjects.

5 | CONCLUSIONS

Patients with haemophilia A, or caregivers, were somewhat satisfied with their current treatment using FVIII concentrate in Korea. However, the study showed that they are less satisfied in terms of the convenience of treatment and that the preference is for simpler and easier characteristics of treatment. Drug characteristics which enhance treatment convenience, such as lower frequency of drug administration and RCD types, should be considered in future decisions regarding treatment selection. Strong consideration of convenience would be more likely to improve the overall satisfaction of patients and caregivers with FVIII concentrate treatment, and it is important for physicians to keep this in mind when discussing treatment options with patients. Practices which enhance the treatment satisfaction of patients, considering their preference, should be tried in an effort to increase treatment adherence and compliance to attain the ultimate treatment goals.

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CONFLICT OF INTEREST

This research was sponsored by Pfizer Pharmaceuticals Korea Ltd. Young-Joo Kim, Ji-Soo Shin and Ho-Jin Lee, who are employees of Pfizer Pharmaceuticals Korea, contributed to study conceptualization, methodology, data analysis and preparation of the manuscript. Chung-Mo Nam and Jiyu Sun, who are contracted with Pfizer Pharmaceuticals Korea for statistical analysis, contributed to study methodology and statistical analysis. The other authors have no potential conflicts of interest to disclose.

AUTHORS' CONTRIBUTIONS

Ki Young Yoo, Soon Ki Kim, Young Shil Park, Young-Joo Kim, Ho-Jin Lee and Ji-Soo Shin conceptualized the study. Ki Young Yoo, Soon Ki Kim, Young-Joo Kim and Chung-Mo Nam contributed to methodology. Ki Young Yoo, Young Shil Park, Tai Ju Hwang, Goon Jae Cho, Soon Ki Kim, Sang Kyu Park, Ji Yoon Kim and Hee Jo Baek investigated (data collection). Chung-Mo Nam, Jiyu Sun and Young-Joo Kim involved in formal analysis. Ki Young Yoo supervised the study. Young-Joo Kim and Ho-Jin Lee contributed to project administration. Ki Young Yoo, Young Shil Park and Young-Joo Kim wrote (original draft). Ki Young Yoo, Young Shil Park, Tai Ju Hwang, Goon Jae Cho, Soon Ki Kim, Sang Kyu Park, Ji Yoon Kim and Hee Jo Baek wrote (review and editing). Young-Joo Kim visualized the study.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available from Pfizer Pharmaceuticals Korea Ltd. Restrictions apply to the availability of these data, which were used under license for this study.

ORCID

Young Shil Park  <https://orcid.org/0000-0002-6643-4245>
 Soon Ki Kim  <https://orcid.org/0000-0002-4785-1705>
 Hee Jo Baek  <https://orcid.org/0000-0003-3830-8134>
 Young-Joo Kim  <https://orcid.org/0000-0003-4914-7305>
 Chung-Mo Nam  <https://orcid.org/0000-0003-0985-0928>
 Ki Young Yoo  <https://orcid.org/0000-0003-1470-3519>

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Characteristics	Effectiveness			Side effects			Convenience			Global satisfaction		
	Mean	SD	Coef.	p	Mean	SD	Coef.	p	Mean	SD	Coef.	p
Both	62.9	14.4			96.8	10.5			54.8	14.2		
RCD type												
PDC syringe	66.0	14.7		.753 (b)	94.7	10.1		<.0001 (c)	62.6	17.8		.067 (b)
Pref. syringe connected with a vial	63.7	14.7			94.9	13.7			57.1	14.4		
Two connected vials	64.7	13.6			98.7	6.1			56.7	14.5		
Diluent volume												
≤5 ml	64.9	13.8		.344 (b)	97.9	7.9		.763 (c)	57.2	14.8		.147 (b)
6–10 ml	62.3	9.5			98.7	3.6			62.5	13.6		
11–20 ml*	50.0	NA			100				38.9			
Others	61.3	16.0			95.8	12.1			53.3	14.8		
Number of vials per injection												
1	63.3	11.7		.278 (b)	96.5	10		.505 (c)	57.5	15.5		.116 (b)
2	64.4	13.7			98.3	6.5			58.4	14.7		
3	65.9	13.4			97.8	9.1			56.5	14.1		
≥4	62.8	17.4			96.9	9.7			52.1	16.1		
Frequency of drug administration												
≥Twice a week	63.4	13.2		.001 (b)	97.5	8.7		.226 (c)	56.7	14.5		.540 (b)
Once a week	64.6	13.0			98.2	7.4			57.2	15.2		
≤Twice a month	73.0	16.1			99.6	2.6			59.7	15.8		
Dose of treatment	505	100		-.002 (a)	.719 (a)			-.001 (a)	.871 (a)			-.001 (a)
Number of bleeding events				-.014 (a)	.002 (a)			-.008 (a)	.068 (a)			-.001 (a)

(a) *p*-value by Spearman's correlation analysis; (b) *p*-value by Mann-Whitney U test; (c) *p*-value by Kruskal-Wallis test. Abbreviations: BMI, body mass index; PDC, prefilled dual chamber; Pref., prefilled; RCD, reconstitution device. * *N* = 1.