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ORIGINAL ARTICLE

Enhanced pharmacokinetics and reduced bleeds in boys with hemophilia A after switching to Kovaltry from other standard half-life factor VIII concentrates

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Abstract

Background: BAY81-8973 (Kovaltry; Bayer, Berkeley, CA, USA) was reported with enhanced pharmacokinetic (PK) profiles compared with some other standard half-life (SHL) factor VIII (FVIII) concentrates. Limited head-to-head comparative studies were conducted in a real-world setting.

Objective: To make head-to-head comparisons of PK and clinical outcomes between Kovaltry and three other SHL FVIII concentrates.

Methods: Forty-seven boys with severe hemophilia A were enrolled and divided into three groups according to their previously used FVIII concentrates (Kogenate FS, N = 22; Advate, N = 14; GreenMono, N = 11). Two separate PK tests were conducted in each participant with a five-point assay during the study period from 6 months before switching to 6 months after switching. FVIII levels were detected by one-stage assay, and PK profiles were calculated by noncompartmental assay. Annualized bleeding rates were collected through participant' bleed logs.

Results: Longer half-life time (Kogenate FS group: 14.4 vs 11.9 hours, $P < .0001$; Advate group: 13.4 vs 9.7 hours, $P < .0001$; GreenMono group: 15.1 vs 10.7 hours, $P < .001$]) and lower clearance (Kogenate FS group: 3.3 vs 3.9 mL/kg/h, $P < .01$; Advate group: 3.7 vs 5.9 mL/kg/h, $P < .01$; GreenMono group: 3.0 vs 5.1 mL/kg/h, $P < .01$) were observed with Kovaltry. In addition, longer mean residential time ($P < .01$) and higher area under the curve ($P < .01$) were demonstrated. No statistical difference was found in in vivo recovery between Kovaltry and the other FVIII products. Participants who switched to Kovaltry from three other FVIII concentrates with the same dosing regimens obtained higher trough FVIII levels and better protection with reduced annualized bleeding rates.

Conclusion: Compared with Kogenate FS, Advate, and GreenMono, Kovaltry showed enhanced PK profiles, which contributed to reduced bleeding rates.

Kun Huang and Yingzi Zhen contributed equally to this work.

KEYWORDS
bleeding, child, factor VIII, hemophilia, pharmacokinetics

Essentials

1. Kovaltry is a standard half-life factor VIII (FVIII) concentrate with enhanced pharmacokinetics.
2. A head-to-head comparison of Kovaltry and other FVIII concentrates was conducted.
3. Enhanced pharmacokinetics and reduced bleeding rates were observed after switching to Kovaltry.
4. Patients with a higher von Willebrand factor level/blood group non-O benefit more.

1 | INTRODUCTION

Hemophilia A is a rare inherited bleeding disorder caused by deficiency of coagulation factor VIII (FVIII). The mainstay of this disease is to give exogenous infusions of FVIII concentrates regularly, which was designed to keep a detectable trough FVIII level and defined as prophylaxis.[1] The traditional target FVIII level (1 IU/dL) in prophylaxis was proposed on the basis of the phenomenon that patients with a milder type (FVIII baseline >1 IU/dL) showed decreased spontaneous bleeds and less joint damage.[2] Collins et al[3] revealed that the bleeding rates were correlated with the average time spent with low FVIII level.

The first prophylactic regimen was proposed in Sweden with a dosage of 25 to 40 IU/kg and frequency of three times per week to every other day based on the principle that the half-life of FVIII is fixed around 12 hours.[4] However, due to the great interindividual variability of pharmacokinetic (PK) profiles, patients with similar dosing regimens could have different FVIII levels during their routine prophylaxis.[3,5,6] This also explained the different clinical outcomes of patients with same dosing regimen. Therefore, the importance of having knowledge of PK profiles among widely used FVIII concentrates was also demonstrated.[7,8]

Although some extended half-life FVIII products with advanced technology were developed to enhance the therapeutic performance, none of them was available in China.[9] This limited access to advanced products was not rare in many developing countries.[10] Thus, many patients still have to make a choice in a list of limited standard half-life FVIII products, either derived from human plasma or produced by genetic engineering. Compared with a few other available standard half-life FVIII concentrates, Kovaltry (BAY81-8973; Bayer, Berkeley, CA, USA) was reported to have enhanced PK parameters like longer half-life ($t_{1/2}$) and lower clearance, which might make it a potentially optimal choice for patients to take over other standard half-life (SHL) FVIII concentrates.[11] In China, Kovaltry was approved to treat hemophilia A in 2018. Although it has the same amino acid sequence as Kogenate FS, its glycans with higher branched structures and sialylation seemed to improve therapeutic performance by enhanced PK profiles.[12] Due to the withdrawal of Kogenate FS (Bayer,Berkeley, CA, USA), patients using Kogenate FS had to switch to Kovaltry or other FVIII products to continue prophylaxis. This special situation led to this study, which aimed to compare the PK profiles of these three widely used SHL FVIII concentrates with Kovaltry in a head-to-head design and check the clinical outcomes of our patients during this switch.

2 | MATERIALS AND METHODS

The study was a pilot report of an investigator-initiated study (ChiCTR2000037821) and approved by the Ethics Committee of Beijing Children's Hospital based on the Declaration of Helsinki. Written informed consent was obtained from each participant and their legally authorized guardian.

2.1 | Study design

This is a prospective, observational study with a head-to-head design to compare the PK profiles and clinical outcomes of Kovaltry and three other SHL FVIII concentrates. Due to the withdrawal of Kogenate FS and the launch of Kovaltry, which was reported with enhanced PK profiles, a few patients switched from other FVIII concentrates to Kovaltry. Eligible patients who switched from other SHL FVIII concentrates to Kovaltry were enrolled. After at least three infusions of Kovaltry, they received a five-point PK test as they did before switching. After the switch, participants were asked to keep their previous prophylactic regimen for at least 6 months. The bleeding rates (annualized bleeding rate [ABR]; annualized joint bleeding rate [AJBR]; and annualized spontaneous bleeding rate [ASBR]) were generated from their bleed logs from 6 months before switching to 6 months after switching.

2.2 | Participants

Boys with severe hemophilia A were enrolled from August 2019 to September 2020 at Beijing Children's Hospital. The inclusion criteria were age <18 years; a definitive diagnosis of severe hemophilia A (FVIII activity level <1 IU/dL); taking plasma-derived or recombinant FVIII concentrates for >50 exposure days; current FVIII inhibitor negative (<0.6 BU/mL, confirmed by two separate tests); receiving other standard half-life FVIII concentrates for at least 6 months

before switching to Kovaltry; switched to Kovaltry with the same or similar dosing regimen for >6 months. Exclusion criteria were the existence of a FVIII inhibitor (≥0.6 BU/mL), fever or active bleeding at inclusion, or a concurrent coagulation disorder. FVIII inhibitor tests were conducted every 3 months for each enrolled participant.

2.3 | Blood samples

For each PK test, peripheral venous blood samples were collected using two 2-mL Vacutainer tubes (3.2% trisodium citrate) after a washout period of at least 72 hours. A previously validated blood-sampling assay (before dosing and 1, 9, 24, and 48 hours after infusion) was used for PK analysis. After blood collection, the samples were immediately centrifuged at 2500 *g* for 15 minutes at room temperature. The platelet-poor plasma was stored at −80°C until all samples were ready for further analysis.

2.4 | Laboratory assay

The one-stage–based activated partial thromboplastin time (aPTT) assay was used to measure FVIII activity in a multidilution mode, with HemosIL FVIII deficient plasma (Instrumentation Laboratory, Bedford, MA, USA). The aPTT reagent was HemosIL SynthAsil (Instrumentation Laboratory). The Nijmegen modification of the Bethesda assay was used for determining the levels of FVIII inhibitors. von Willebrand factor antigen (VWF:Ag) level were detected with a latex particle-enhanced immunoturbidimetric assay using the HemosIL VWF:Ag kit (Instrumentation Laboratory). The ACL TOP-700 analyzer (Instrumentation Laboratory) was used to perform all measurements.

2.5 | PK analysis

PK analysis was conducted by WinNonlin software (Pharsight Corp., Mountain View, CA, USA) with a noncompartmental assay. The individualized PK profiles followed were estimated: terminal half-life time ($t_{1/2}$), clearance (CL), area under the curve (AUC), mean residence time (MRT) after intravenous injection. In vivo recovery (IVR) was calculated as follows: IVR (IU/dL per IU/kg) = (C_{max}–$FVIII_{preinfusion}$) (IU/dL)/($FVIII_{administered}$ [IU/dL]/body weight [kg]).[13] The trough FVIII level was calculated through their dosing regimen (dose and frequency) and individualized PK parameters.

2.6 | Clinical outcomes

The bleeding rates (ABR, AJBR, and ASBR) were calculated as well as zero bleeding rates (ZBR; zero joint bleeding rate [ZJBR]; and zero spontaneous bleeding rate [ZSBR]) according to their bleeding record from 6 months before switching to 6 months after switching.

2.7 | Statistical analysis

The statistical analysis and the figure generation were performed using Prism for Mac version 9.1.1 (GraphPad Software, La Jolla, CA, USA). Normally distributed data were reported as mean ±standard deviation, while nonnormally distributed data were reported as median (upper quartile, lower quartile). When necessary, range of the data was also provided. One-way analysis of variance and *t* tests were employed to evaluate the difference among normally distributed data; for nonnormally distributed data, Kruskal-Wallis and Mann-Whitney tests were used to evaluate the difference. Pearson (normally distributed data) or Spearman (nonnormally distributed data) correlation coefficients were used to analyze the potential relations between PK parameters and the characteristics of participants or bleeding rates. *P* values <.05 indicated a statistically significant difference.

3 | RESULTS

3.1 | Participant demographics

In total, 62 boys were screened, and 50 were eligible for participation. Three were ruled out because of poor adherence. As a result, 47 participants were enrolled in this study. Of these participants, 22 switched from Kogenate FS, 14 switched from Advate (Shire, Westlake Village, CA, USA), and the other 11 boys switched from GreenMono (GreenCross, Yongin, Korea) for prophylaxis. Participants' age at their switch were, respectively, 6.4 ± 2.8 years, 6.4 ± 2.6 years, and 5.4 ± 2.7 years. The median weight of patients in these three groups were 21.2 kg (Kogenate FS), 25.5 kg (Advate), and 18.0 kg (GreenMono). The median time from their first PK test to the Kovaltry PK test were 10.0 (7.8-12.0) months for Kogenate FS, 9.5 (5.8-10.3) months for Advate and 8 (6.0-12.0) months for GreenMono. There were 13 participants with blood type O in the Kogenate FS group, and the corresponding number was 8 in the Advate group and 5 in the GreenMono group. Detailed information on participant characteristics is found in Table 1. No participant developed FVIII inhibitor during the study period.

3.2 | Individualized PK parameters of different FVIII concentrates

In our study, Kovaltry showed a prolonged $t_{1/2}$ in patients who switched from Kogenate FS (14.4 vs 11.9 hours, $P < .001$), Advate (13.4 vs 9.6 hours, $P < .0001$), and GreenMono (15.1 vs 10.7 hours, $P < .001$). For IVR, although no statistical difference was found in these three groups during the switch, the trend of increased IVR could be noted in the Advate group (1.7 vs 1.6, $P=.06$) and the GreenMono group (1.9 vs 1.7 IU/kg per IU/dL, $P = .08$). Compared with Kovaltry, decreased weight-adjusted CL was observed in Kogenate FS (3.3 vs 3.9 mL/kg/h, $P < .01$), Advate (3.7 vs 5.9 mL/

TABLE 1 Patient characteristics

		Kogenate FS (N = 22)	Advate (N = 14)	GreenMono (N = 11)
Race, Chinese (100%)		Chinese	Chinese	Chinese
Age, y	Median/mean	6.4 ± 2.8	6.4 ± 2.6	5.4 ± 2.7
	Range	2.6–12.0	2.9–10.6	1.7–9.9
Weight, kg	Median/mean	21.2 (16-30)	25.5 (12.1-31)	18.0 (15-25)
	Range	13-56	15-46	12-43
Body mass index, kg/m^2	Median/mean	16.0 (14.6-17.4)	16.3 (14.5-18.2)	15.7 (13.3-17.8)
	Range	8.9-27.4	13.0-21.6	11.5-26.4
VWF:Ag, IU/dL	Median/mean	91.2 ± 29.3	93.2 ± 27.9	95.3 ± 25.4
	Range	40.5-163.3	57.4-143.5	65.4-139
Blood group, O:non-O	Number of patients	13:9	8:6	5:6
Time period between two PKs (month)	Median/mean	10 (7.75-12)	9.5 (5.75-10.25)	8 (6-12)
	Range	5-12	3-11	4-12

Abbreviation: VWF:Ag, von Willebrand factor.

TABLE 2 Individualized pharmacokinetic parameters of different FVIII concentrates

		Kogenate FS		Advate		GreenMono	
		Mean/Median	Range	Mean/Median	Range	Mean/Median	Range
Half-life time, h	Before switch	11.9 ± 2.4	7.1-16.1	9.7 ± 1.7	7.5–12.5	10.7 ± 1.7	8.1-13.9
	After switch	14.4 ± 2.9	7.1–20.4	13.4 ± 1.4	11.6-16.0	15.1 ± 3.4	11.3-22.6
	P value	<.0001		<.0001		<.001	
IVR, IU/kg per IU/dL	Before switch	1.8 (1.6-2.1)	1.5–3.2	1.6 (1.5-1.8)	1.3–2.1	1.7 (1.6-1.9)	1.3-2.0
	After switch	1.8 (1.6-1.9)	1.4-2.7	1.7 (1.7-1.8)	1.5-2.2	1.9 (1.7-2.2)	1.6-2.6
	P value	.16		.06		.08	
CL, mL/kg/h	Before switch	3.9 ± 1.2	1.6-5.3	5.9 ± 2.2	2.3–10.1	5.1 ± 1.6	2.9-8.1
	After switch	3.3 ± 1.1	1.5-5.9	3.7 ± 1.2	1.4–6.3	3.0 ± 1.2	1.4-6.0
	P value	<.01		<.01		<.01	
AUC, IU h/dL	Before switch	1316 (1045-1696)	756-3192	936 (750-1104)	476-1993	1058 (811-1300)	751-2600
	After switch	1638 (1250-1899)	842–3635	1504 (1298-1688)	1013-2921	1650 (1300-2201)	981-3836
	P value	<.01		<.001		<.01	
MRT, h	Before switch	14.6 ± 3.8	8.3-22.7	11.7 ± 2.2	8.1-15.1	12.9 ± 3.4	8.6-20.3
	After switch	18.3 ± 4.2	7.5-24.6	17.1 ± 2.4	13.2-21.4	19.3 ± 5.7	10.1-30.9
	P value	<.0001		<.0001		<.01	

Note: Data are depicted as median (lower quartile–upper quartile) with range except for IVR and AUC, which are shown as mean ± standard deviation.

Abbreviations: AUC, area under the curve; CL, clearance; FVIII, factor VIII; IVR, in vivo recovery; MRT, mean residential time.

kg/h, $P < .001$), and GreenMono (3.0 vs 5.1 mL/kg/h, $P < .01$). In addition, higher AUC ($P < .01$) and longer MRT ($P < .01$) were also demonstrated in all three FVIII groups. All the detailed descriptions of individualized PK profiles among these SHL FVIII concentrates are depicted in Table 2.

3.3 | Half-life time augment in relationship to endogenous VWF:Ag level and blood groups

The relationship between $t_{1/2}$ augment and endogenous VWF:Ag level was investigated. The result showed that the $t_{1/2}$ augment had

a positive relationship with the endogenous VWF:Ag level, which was observed in the Kogenate FS group ($r = .61$, $P < .01$), the Advate group ($r = .54$, $P < .05$), and the GreenMono group ($r = .72$, $P = .01$; Figure 1). In addition, patients with blood type O seemed to have a shorter $t_{1/2}$ augment compared with those participants with non-O blood type. This phenomenon of "blood type O's disadvantage" could be found in the Kogenate FS group (2.6 vs 2.1 hours, $P < .05$), the Advate group (2.5 vs 4.3 h, $p < 0.05$), and the GreenMono group (2.1 vs 5.0 hours, $P < .05$; Figure 2).

3.4 | Dosing regimen, trough level, and bleeding rates during the switch

In our study, participants were asked to keep the same dosing regimen during the switch. The dose and frequency of participants in the Kogenate group were 19.62 (16.84-28.41) IU/kg each infusion and 3 (2.25-3.5) infusions per week, while the participants in the Advate group had a higher dose of 28.22 (22.48-33.52) IU/kg each infusion and a frequency of 3.5 (3-3.5) infusions weekly. Because GreenMono is a plasma-derived FVIII concentrate with a different vial size than the other recombinant SHL FVIII products, participants doses were calculated according to their routine prophylactic treatment record. In spite of the different vial size of GreenMono, the dose of Kovaltry in these 11 participants was not statistically different from their former dose (20.83 [20-27.78] vs 23.07 [16.66-25.0] IU/kg, $P = .85$) at each infusion of GreenMono, which also could be reflected by the very near average dose (22.25 vs 22.58 IU/kg) of each infusion. The frequency of participants in the GreenMono group remained 3 (2-3) infusions per week during the study period. Due to the enhanced individualized PK profiles of Kovaltry, the participants with trough level <1 IU/dL decreased from 11 to 6, while the patients with a trough level of 1 to 3 IU/dL and >3 IU/dL escalated from 8 to 10 and from 3 to 6, respectively. Similar improvements in the other two groups are clearly described in Table 3.

The bleeding rates were collected as the indicators of clinical outcomes during the switch. After switching to Kovaltry with the same dosing regimen, reduced ABRs were observed in the Kogenate FS group (4 [0-6.5] vs 4 [1.5-8.5], $P < .05$), the Advate group (2 [0-5.5] vs 4 [1.75-7.5], $P < .05$) and the GreenMono group (4 [2-8] vs 6 [4-12], $P < .01$). In the Kogenate group, no statistically significant difference in AJBR ($P = .11$) and ASBR ($P = .06$) was revealed after switching to Kovaltry. In the Advate group, improved AJBR (1 [0-2.5] vs 2 [0-5], $P < .05$] and ASBR (0 [0-2] vs 0 [0-4], $P < .05$) were observed. Similarly, statistically reduced bleeding rates were also noticed in the GreenMono group (Table 3). In addition, higher zero bleeding rates were also noticed. Higher ZBR (Kogenate FS group, 36% vs 23%; Advate group, 29% vs 14%; GreenMono group, 18% vs 10%), ZJBR (GreenMono group, 36% vs 18%) and ZSBR (Kogenate FS group, 68% vs 60%; Advate group, 71% vs 57%; GreenMono group, 55% vs 27%). Figure 3 shows the detailed bleeding rates by individuals.

4 | DISCUSSION

As previously reported, the great interindividual variability in the PK profiles of FVIII concentrates leads to different trough levels in patients with the same dosing regimens for prophylaxis.[3,8,13] Thus, the knowledge of widely used FVIII concentrates' PK profiles is vital for a better understanding of the prophylactic regimen in routine prophylaxis and on-demand infusions. Due to the limited access to improved products like extended $t_{1/2}$ FVIII concentrates as well as the poor affordability, our patients still have to accept prophylaxis with SHL FVIII products, which had a short $t_{1/2}$ of around 8 to 12 hours. This not only led to the heavy burden on frequent intravenous infusions, but also limited the possibility to achieve a high trough level, which might be important for a few patients in need. In some previous studies, Kovaltry was reported with enhanced PK profiles, which might bring improved clinical outcomes compared with other SHL FVIII concentrates.[14] Hence, this comparative study of pharmacokinetics and clinical outcomes between Kovaltry and the other three most-used SHL FVIII concentrates was conducted to evaluate the real-world switch in China.

Compared with its former generation recombinant FVIII (rFVIII) concentrate (Kogenate FS), Kovaltry had some enhanced PK parameters like longer $t_{1/2}$, low CL, and higher AUC and MRT. An average $t_{1/2}$ augment of 2.5 hours (14.4 vs 11.9 hours) was detected in our study. Similar results could be found in other studies. In well-designed LEOPOLD (Trial to Evaluate the Efficacy and Safety

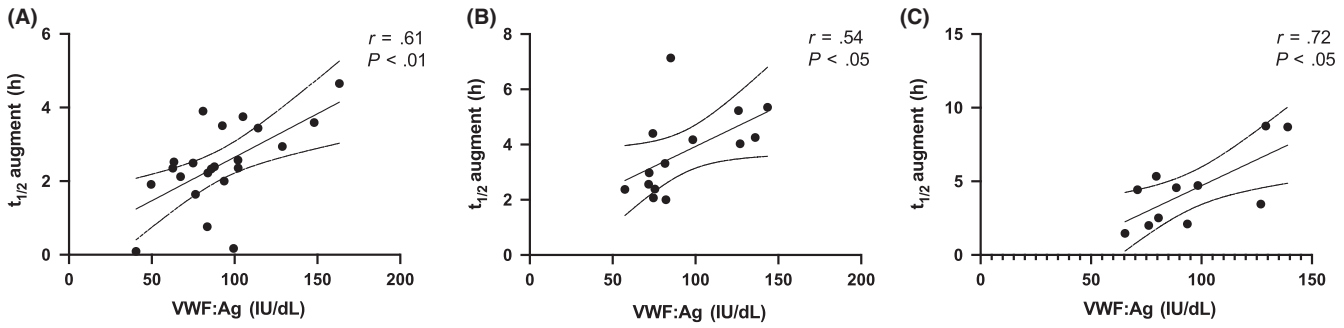

FIGURE 1 Relationship between $t_{1/2}$ augment and VWF:Ag level in (A), Kogenate FS group; (B), Advate group; and (C), GreenMono group. $t_{1/2}$, half-life; VWF:Ag, von Willebrand factor antigen

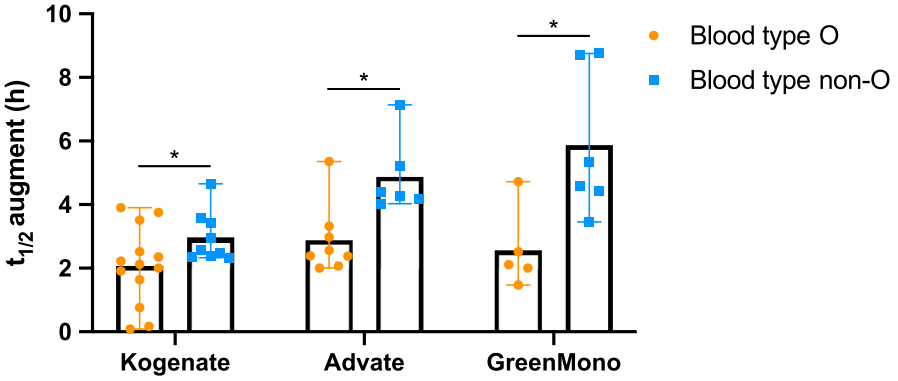

FIGURE 2 Comparison of $t_{1/2}$ augment in patients with different blood groups. $t_{1/2}$, half-life

TABLE 3 Trough FVIII level and bleeding rates of three FVIII concentrate groups

		Kogenate		Advate		GreenMono	
		Median (lower-upper quartile)	Mean (range)	Median (lower-upper quartile)	Mean (range)	Median (lower-upper quartile)	Mean (range)
ABR	Before switch	4 (1.5-8.5)	4.91 (0-14)	4 (1.75-7.5)	5.64 (0-16)	6 (4-12)	7.45 (0-16)
	After switch	4 (0-6.5)	3.90 (0-12)	2 (0-5.5)	4.0 (0-14)	4 (2-8)	4.36 (0-10)
	P value	.04		.02		.004	
AJBR	Before switch	0 (0-4)	2.18 (0-8)	2 (0-5)	3.14 (0-12)	4 (2-8)	5.01 (0-16)
	After switch	0 (0-4)	1.55 (0-6)	1 (0-2.5)	1.71 (0-8)	2 (0-6)	2.54 (0-8)
	P value	.11		.05		.01	
ASBR	Before switch	0 (0-4)	1.54 (0-6)	0 (0-4)	2.0 (0-8)	2 (0-6)	3.64 (0-10)
	After switch	0 (0-2)	0.86 (0-4)	0 (0, 2)	0.57 (0-2)	0 (0, 2)	1.27 (0-4)
	P value	.06		.03		0.008	
Trough level<1%	Before switch	11		6		8	
	After switch	6		3		4	
Trough level 1%-3%	Before switch	8		6		3	
	After switch	10		3		4	
Trough level >3%	Before switch	3		2		0	
	After switch	6		8		3	

Note: Paired Wilcoxon tests were used to do the comparisons.

Abbreviations: ABR, annualized bleeding rate; AJBR, annualized joint bleeding rate; ASBR, annualized spontaneous bleeding rate; FVIII, factor VIII.

of a New Full Length Recombinant Human FVIII for Hemophilia A) studies, the PK parameters of Kogenate FS and Kovaltry were also compared, and parallel results were observed. Longer $t_{1/2}$, higher AUC, and lower CL were clearly revealed in Kovaltry in these long-term clinical trials.[15-17] In addition, in the study by Megías-Vericat et al,[18] which also had a crossover design to make the comparison in 14 adults, longer $t_{1/2}$ of Kovaltry (16.9 vs 15.4 hours) was demonstrated. Considering their older age distribution (median, 30.1 [range, 10–50] years), it is also reasonable to obtain shorter $t_{1/2}$ results in our pediatric patients with a median age around 6 years. Since Kovaltry used an identical amino acid sequence to Kogenate FS, the 20% increase in $t_{1/2}$ might come from its innovative techniques in production. According to Teare et al,[12] Kovaltry had higher levels of sialylation (96%) than Kogenate FS (94%) and Advate (78%-81%). This increased N-linked glycan branching with a high level of sialylation might contribute to the improved PK profiles. The comparison of Advate and Kovaltry was also conducted in our study. Significantly longer $t_{1/2}$ and lower CL as well as higher AUC and prolonged MRT after a single dose of infusion could be noted in these 14 boys with hemophilia A switched from Advate to Kovaltry. This was in accordance with the randomized PK study reported by Shah et al in 2017.[15] Except for these two rFVIII concentrates, the Chinese mostly used a plasma-derived FVIII product named GreenMono, which was also studied. The data of the 11 participants switched from GreenMono to Kovaltry also indicate the advantages of this change through enhanced PK profiles like the much longer $t_{1/2}$ (15.1 vs 10.7 hours) as well as lower CL (3.0 vs 5.1 mL/kg/h). The IVR of Kovaltry in our study was similar to previously reported data (1.7-1.9 vs. 1.8 IU/kg per IU/dL).[19] Although the IVR did not show a statistical difference between Kovaltry and the other three SHL FVIII concentrates, the trend of increased IVR in Kovaltry compared with Advate (median, 1.7 vs 1.6 IU/kg per IU/dL) and GreenMono (median, 1.9 vs 1.7 IU/kg per IU/dL) still could be noticed.

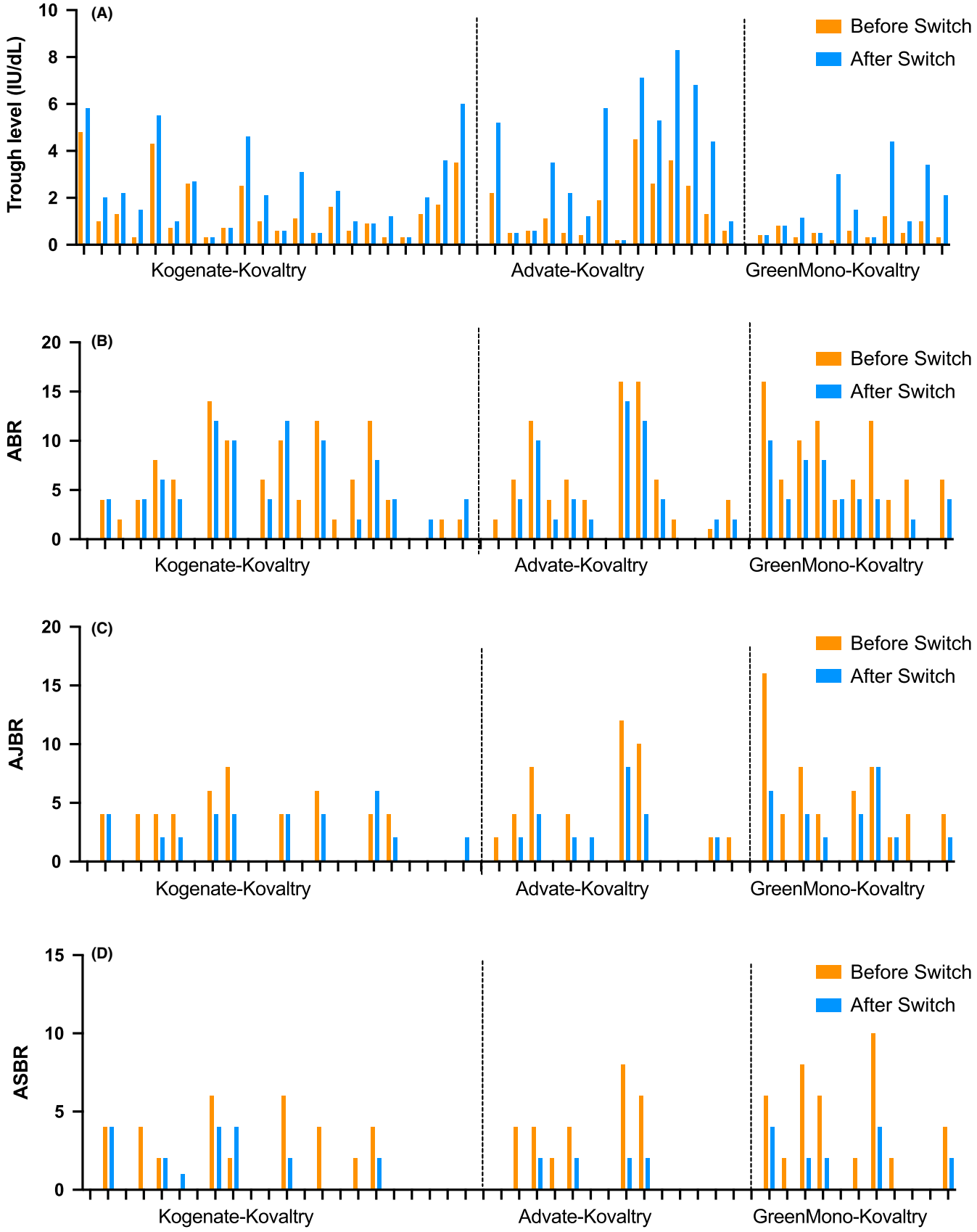

FIGURE 3 (A) Individual comparisons of trough level during the switch. (B) Individual comparisons of annualized bleeding rate (ABR) during the switch. (C) Individual comparisons of annualized joint bleeding rate (AJBR) during the switch. (D) Individual comparisons of annualized spontaneous bleeding rate (ASBR) during the switch

The relationship between the $t_{1/2}$ augment and VWF:Ag level/blood group was also investigated. The results showed that individuals with a higher exogenous VWF:Ag level tend to obtain a longer $t_{1/2}$ augment. Also, participants with blood group O seemed to benefit more from the switch with a longer $t_{1/2}$ augment compared with those with blood group non-O. As is well known, the circulation $t_{1/2}$ of FVIII is influenced by VWF:Ag level due to their combination.[20] Dissociative FVIII molecules have an extremely short $t_{1/2}$ of ≈2 hours, which indicates that the final $t_{1/2}$ of FVIII is also determined by the metabolism of VWF:Ag. According to Swystun et al,[21] the PK profile of VWF:Ag is the key impactor on $t_{1/2}$ of FVIII, and mutations in the specific area of the VWF:Ag gene that encodes its binding region to FVIII protein have an influence on $t_{1/2}$ of injected FVIII concentrates as well. Considering the fact that individuals with blood type O usually had lower exogenous VWF:Ag levels, it is also not surprising to find they had a shorter $t_{1/2}$ augment during the switch. This observation might give a hint that individuals with high VWF:Ag levels or non-O blood groups could expect more improvements of PK profiles and therefore potential reduction in bleeds or longer intervals as well as less frequent infusions.

Due to the enhanced parameters, individuals with the same dosing regimen obtained higher trough levels and less time with low FVIII level in routine prophylaxis. In all three groups, the number of participants with trough levels <1 IU/dL decreased by ≈50% (Kogenate FS, 11 to 6; Advate, 6 to 3; GreenMono, 8 to 4). As a result, higher trough levels were observed in most participants, which might bring improved clinical outcomes like reduced bleeding rates. In our study, statistically improved ABR, AJBR, and ASBR were all demonstrated in the Advate group and the GreenMono group during the study period. Considering the same dosing regimen during the switch in the Kogenate FS/Advate group and the GreenMono group (22.25 vs 22.58 IU/kg; same frequency), the improvements of bleeding rates are mostly attributed to the enhanced PK profiles, such as prolonged $t_{1/2}$ and decreased CL. In addition, the higher AUC of Kovaltry also indicates the potential to reduce preclinical bleeds that could only be detected by advanced imaging technology like magnetic resonance imaging and ultrasound. Although not investigated in this study, previous research has revealed the potential relationship between AUC in routine prophylaxis and preclinical bleeds as well as joint damage.[22] Despite the lack of statistical improvement of ASBR in the Kogenate FS group, its trend of reduction could still be noticed by decreased average values (0.86 vs 1.54). Parallel results could be found in other studies. A comparative cross-sectional study observed statistically reduced ABR, AJBR, and ASBR in their 14 participants with hemophilia A. In another large real-world study that investigated the switch to Kovaltry from other SHL FVIII concentrates with similar dosing regimens, Arvanitakis et al[23] also demonstrated decreased ABR (0.4 vs 1.1) and AJBR (0.3 vs 0.7) as well as the escalated zero bleeding rate (82.5% vs 75%).

The main limitation of our study was the time period of two PK tests (median, 8-10 months). The best way to compare the PK profiles of two FVIII concentrates is to limit the time period of two PK tests as much as possible, which is hardly possible in a real-world setting. However, according to previous studies, the increase of $t_{1/2}$ with age was as slow as ≈0.4 hour per year. Also, this head-to-head comparison with crossover design in our study ensured the comparability since the interindividual variability was avoided because the participants acted as their own controls. Considering all the above, our results and conclusion are still valid.

5 | CONCLUSION

In conclusion, our study revealed the enhanced PK profiles and improved clinical outcomes of Kovaltry compared with three other most-used SHL FVIII concentrates in China. This valuable PK data of children with hemophilia A could be further used to build a population PK model and conduct PK-tailored prophylaxis in the future.

RELATIONSHIP DISCLOSURE

The authors stated that they had no interests that might be perceived as posing conflict or bias.

AUTHOR CONTRIBUTIONS

KH enrolled patients, conducted PK tests, analyzed the data, and drafted the manuscript. YZ and XW devoted to blood sampling. GL did the laboratory tests. ZC and RW designed the study, reviewed the manuscript, and approved the submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon reasonable request to the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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