ORIGINAL ARTICLE

WILEY

Real-world use of emicizumab in Chinese children with hemophilia A: Retrospective data from a comprehensive care center

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ABSTRACT

Importance: Emicizumab (EMI) is efficacious and safe for hemophilia A (HA) prophylaxis. However, its high cost poses a challenge in China.

Objective: To explore the possibility of using reduced-dosage EMI in Chinese HA children.

Methods: We conducted a retrospective study for HA children in our Comprehensive Care Center. Data were collected pre- and post-EMI treatment to evaluate bleeding rates. Laboratory analyses included factor VIII (FVIII)-like activity and EMI concentration measurements.

Results: Thirty-four HA children receiving EMI prophylaxis for a median (range) 24.5 (2.5–47.9) months by June 2023. Of these, 25 (73.5%) were under 3 years of age, 26 (76.5%) had severe hemophilia and 12 (35.3%) were minimally treated or previously untreated patients. Thirty-one (91.2%) of the 34 patients received reduced-dosage EMI for economic reasons. EMI concentration and FVIII-like activity measured showed a strong correlation. Overall, while on EMI, their annual treated bleeding rate (ATBR) and annual bleeding rate (ABR) decreased significantly (2–0) while their zero-bleeding rate (ZBR) increased significantly (11.5%–65.4%). After 6 months of EMI, there was no significant difference in ATBR and ABR among various maintenance dosages. However, ZBR was significantly lower in dosages under 4 mg/kg ($P = 0.0156$). Receiver operator characteristic curves suggested the following cutoff values for zero bleeding: EMI 4-weekly maintenance dosage 3.8 mg/kg, EMI concentration 48.1 μg/mL, and FVIII-like activity 15.4 IU/dL.

Interpretation: We showed EMI effectively prevented bleeding even at reduced dosages. However, the bleeding risk may be higher with EMI 4-weekly maintenance dosage <3.8 mg/kg, EMI concentration <48.1 μg/mL, and FVIII-like activity <15.4 IU/dL for zero bleeding. It is important that dosage reduction be done rationally. Dosage tailoring is possible.

DOI: 10.1002/ped4.12439

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Funding source
National Natural Science Foundation of China, Grant/Award Number: 82270133

Received: 24 December 2023
Accepted: 4 June 2024

KEYWORDS
Hemophilia A, Emicizumab, Prophylaxis

INTRODUCTION

Emicizumab (EMI, Roche; Hemlibra) is a groundbreaking medication developed for the prophylactic treatment of hemophilia A (HA). Up to now, the cornerstone treatment for HA involved intravenous replacement therapy, where the missing factor VIII (FVIII) was substituted. EMI is a recombinant humanized bispecific monoclonal antibody that acts as a bridge between factor IXa and Factor X (FX) simulating the cofactor function of FVIII for activating FX–FXa. It is administered via subcutaneous injection. Initially approved by the Food and Drug Administration for patients with HA and inhibitors, it received further approval in October 2018 for prophylaxis in patients with HA without inhibitors.[1] The use of EMI has shown dramatic improvements in patient outcomes, with many patients experiencing zero bleeds.

The safety and efficacy of EMI have been verified in seven clinical trials,[2] and EMI is increasingly used in Europe and North America. However, in developing countries like China, EMI is not yet covered by medical insurance, so many families bear the full cost of the medication which represents a heavy financial burden. This article mainly focuses on the following questions: Can the dosage of EMI be reduced? How can the EMI dosage be reduced? Currently, in China, most children who use EMI have elected to use reduced dosages. Even infants with very low body weight might not be receiving the full standard EMI dosage of 6 mg/kg every 4 weeks. A retrospective analysis of the real-world data from our patients may provide answers to these questions. The aim of this study was to explore the possibility of a more rational reduction plan using EMI and to improve the cost-effectiveness of our patients.

METHODS

Ethical approval

The study was approved by the Ethics Review Board of Beijing Children's Hospital ([2022]-E-166-Y). Informed consent was obtained from the parents or legal guardians of each recruited patient.

Study design and data acquisition

We conducted a retrospective study in June 2023 at Beijing Children's Hospital Comprehensive Care Centre (CCC), gathering real-world data from our pediatric patients with moderate to severe HA undergoing prophylaxis with EMI. We retrieved information prior to EMI treatment from the hospital's historical data system and from patient diaries. We assessed the annual treated bleeding rate (ATBR) as well as the annual bleeding rate (ABR) for a minimum of 6 months before and 6 months after EMI treatment. Zero-bleeding rate (ZBR) was collected for a minimum of 6 months before and 12 months after EMI treatment.

All patients initiated their EMI prophylaxis regimen following a clinic visit. Patients were prescribed a standard loading dosage of EMI at 3.0 mg/kg weekly for 4 weeks, and maintenance EMI dosage at 1.5 mg/kg weekly (QW), or 3.0 mg/kg every 2 weeks (Q2W), or 6.0 mg/kg every 4 weeks (Q4W). Although the patients were prescribed standard dosages, they often reduced their dosage by decreasing the amount per injection or altering the intervals between injections to lower costs during both the loading and maintenance periods.

The first four EMI injections were administered within a hospital setting equipped for managing potential serious allergic reactions and adverse drug events. The study team maintained continuous contact with each participating family to monitor clinical outcomes. EMI concentration and FVIII-like activity were to be measured in all participating patients both during the loading period (assessed just prior to the first maintenance dosage) and during the maintenance period.

ABR and ATBR are defined as the average number of bleeding events per month of follow-up, multiplied by 12. ABR refers to the total number of bleeding episodes per annum, both treated and untreated including subcutaneous

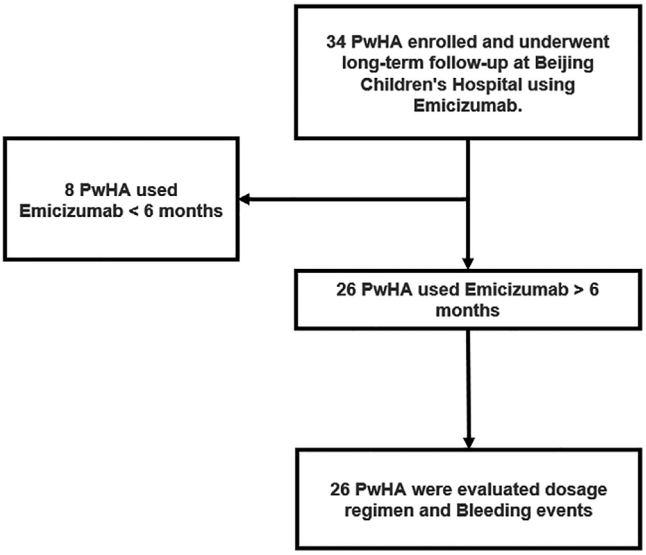

FIGURE 1 Flow chart of the study. PwHA, patients with hemophilia A.

hemorrhages not requiring treatment. ATBR denotes the total number of treated bleeding episodes per annum.[1] ZBR is the percentage of patients who had zero bleeds before and after initiating EMI. The flowchart of patient follow-up in this study is shown in Figure 1.

Laboratory procedures

Blood samples for FVIII inhibitor, EMI concentration, and coagulation activity analyses were drawn into 2 mL vacuum tubes containing 0.109 mol/L buffered citrate during the follow-up visits. After a 15-min centrifugation (RCF 2500 g at 15–25°C), platelet-poor plasma was aliquoted and preserved at −80°C for further testing. FVIII inhibitors were identified using a bovine chromogenic Bethesda assay on an ACL-TOP 700 autoanalyzer. Coagulation activity was measured using a Biophen Plasma Calibrator reagent via a chromogenic assay, with outcomes expressed as FVIII-like activity (IU/dL). EMI concentrations were measured by a modified one-stage clotting assay according to the method of Liu et al.[3] and Pekrul et al.[4]

Statistical analysis

Due to our limited sample size, we represented both normally and non-normally distributed data using the median and range. Differences in non-normal data were assessed using the Wilcoxon's test, Spearman rank correlation analysis, Kruskal-Wallis test, and Chi-Squared Test. A *P*-value less than 0.05 is considered statistically significant. We obtained the equations through linear regression analysis. All of the above analyses and figure representation were conducted using GraphPad Prism for Windows (Version 8.41). We used SPSS for Windows (version 26) to plot the receiver operator characteristic (ROC) curve and maximize Youden's index to find the threshold. Additionally, we utilized bootstrapping to create a distribution of the area under curve values and estimate the confidence intervals. Values are expressed as median (range) unless otherwise stated.

RESULTS

Patient demographics and clinical characteristics

We collected data from 34 patients with a median age of 1.9 (range 0.1–9.1) years and a body weight of 12.5 (4.5–38.0) kg. Of these 34 children, 22 (73.5%) were < 3 years of age, 26 (76.5%) had severe HA (SHA), and 12 (35.3%) were previously untreated (PUP) or minimally treated (MTP) patients. Among the 22 previously treated patients (PTP), eight (36.4%) had inhibitors. Before EMI, the median (range) ATBR was two (0–18). Four (11.8%) of the 34 patients had a history of life-threatening bleeding.

Pharmacokinetic characterization of EMI

We conducted EMI testing in 64 instances. During the loading period, 17 patients were available for FVIII-like activity measurement. All patients were measured at week five (just prior to the start of maintenance dosage) and they all followed the approved QW (one injection per week) regimen. Their median (range) EMI loading dosage was 3.0 (1.5–3.3) mg/kg per week, and their FVIII-like activity was 19.6 (7.6–35.3) IU/dL. Seven of these 17 patients had both EMI concentration and FVIII-like activity measurements performed at the same time. Their median (range) EMI concentration was 51.5 (31.8–65.9) μg/mL and their corresponding median (range) FVIII-like activity was 14.6 (7.6–19.6) IU/dL while receiving a loading dosage of 3.0 mg/kg per week. During the maintenance period, 22 patients received a median (range) dosage of 2.1 (0.8–3.2) mg/kg per injection, with a median (range) interval of median 14 (10–21) days. Their median (range) 4-weekly maintenance EMI dosage was 4.0 (1.6–6.3) mg/kg. They were available for FVIII-like activity measurement, and their corresponding median (range) FVIII-like activity was 15.4 (4.9–30.1) IU/dL. Eighteen of these 22 patients had both EMI concentration and FVIII-like activity performed at the same time. Table 1 shows their EMI concentrations (48.1 μg/mL) and their corresponding FVIII-like activities (14.6 IU/dL) while receiving a 4-weekly maintenance EMI dose of 4.0 mg/kg. In all, 25 patients (seven in the loading period and 18 in the maintenance period) had paired EMI concentration and FVIII-like activity data. Figure 2A shows the good correlation between their plasma EMI concentration and their FVIII-like activity. We further show that for the 18 patients with paired data during the maintenance period, their EMI maintenance dosage also correlated well with both their FVIII-like activity (Figure 2B) and their plasma EMI concentration (Figure 2C).

TABLE 1 Emicizumab (EMI) dosage and regimen, EMI concentration, and factor VIII (FVIII)-like activity for the 18 patients during the maintenance period

Patient	Injection interval (days)	EMI dosage pre-injection (mg/kg)	4-weekly maintenance dosage (mg/kg)	EMI concentration[a] (μg/mL)	FVIII-like activity[a] (IU/dL)
PN-01	14	0.8	1.6	17.8	4.9
PN-02	21	1.9	2.5	29.4	7.1
PN-03	17	2.2	3.6	30.8	7.2
PN-04	14	1.9	3.7	45.0	13.1
PN-05	14	1.3	2.5	41.9	12.2
PN-06	14	1.9	3.8	49.5	15.8
PN-07	21	3.0	4.0	54.6	16.2
PN-08	21	3.0	4.0	47.2	15.0
PN-09	14	2.0	4.2	36.0	10.8
PN-10	14	2.1	4.3	37.7	10.4
PN-11	21	3.2	4.3	52.0	15.8
PN-12	10	1.5	4.3	65.0	19.1
PN-13	15	2.4	4.5	59.0	21.4
PN-14	20	3.2	4.5	83.0	29.0
PN-15	14	2.0	4.0	36.9	8.1
PN-16	14	1.3	2.5	51.4	14.6
PN-17	14	2.8	5.6	49.0	16.7
PN-18	14	3.2	6.3	50.2	14.6

[a]EMI concentration and FVIII-like activity were to be measured in all participating patients during the maintenance period, just before the next injection.

Dosage reduction and influencing factors

During the loading period, only 20 (58.8%) of 34 patients used the full standard weekly EMI dosage of 3.0 mg/kg. Of the 14 (41.2%) patients who used reduced weekly loading dose, 11 (78.6%) used 2.0–3.0 mg/kg, and 3 (21.4%) used < 2.0 mg/kg. During the maintenance period, only three (8.8%) patients used the full standard 4-weekly dosage of 6.0 mg/kg. The remaining 31 (91.2%) patients had their 4-weekly EMI maintenance dosage reduced to 5.0–6.0 mg/kg in 11 (32.4%), 4.0–5.0 mg/kg in 12 (35.3%) and < 4.0 mg/kg in eight (23.5%).

The different risk factors influencing their dosage reduction are available in 29 patients and are shown in Table 2. The other 5 patients declined to disclose why they reduced the dosage due to privacy concerns. Among the risk factors, annual household income was the most prominent factor, with a Spearman correlation of $r_s = 0.4735$ and a significance level of $P = 0.0126$.

Clinical outcomes

The median (range) follow-up period for the 34 patients was 24.5 (2.5–47.9) months with 26 (76.5%) patients followed for more than 6 months. While on EMI, compared to the pre-EMI period, the median (range) ATBR of these 26 patients decreased significantly from 2 (0–18) to 0 (0–2) ($P < 0.0001$), their median (range) ABR decreased significantly from 2.5 (0–18) to 0 (0–4) ($P < 0.0001$) and their annualized ZBR increased significantly from 11.5% to 65.4% ($P < 0.0001$).

We also compared the characteristics and bleeding profiles of PUP/MTP with PTP (Table 3), and those of patients with or without inhibitors (Table 4).

PUP/MTP versus PTP

Twelve (35.3%) of the 34 patients were PUP or MTP patients, of whom 11 (91.7%) were SHA. They started using EMI at a median (range) of 0.9 (0.1–1.6) years. Their 4-weekly EMI maintenance dosage was 4.2 (3.6–5.8) mg/kg. There were 22 (64.7%) PTP patients, of whom 15 (68.1%) were SHA. When compared to the PUP/MTP patients, they started using EMI at a significantly older age ($P < 0.0001$), at 3.5 (0.8–9.1) years. Their 4-weekly EMI maintenance dosage was similar at 4.5 (1.6–6.3) mg/kg ($P = 0.7609$).

TABLE 2 Factors influencing dosage reduction

Variables	4-weekly EMI maintenance dosage (mg/kg)			Spearman (*r*)	*P*
	<4	4–5	>5		
Number of patients[a]	6/8	10/12	13/14	–	–
Current weight (kg)	19.0 (16.0–39.0)	19.0 (11.5–40)	14.5 (7.8–26.0)	−0.3402	0.0710
Having EMI insurance	2/6	1/10	4/13	0.1927	0.3166
Annual therapy cost (10 000 CYN)	25.5 (12.0–45.0)	31.5 (19.5–60.0)	25.0 (5.0–50.0)	−0.0458	0.8135
Annual household income (10 000 CYN)				0.4735	0.0126
≤30	4/6	4/10	1/11		
>30–50	2/6	5/10	6/11		
>50–100	0	1/10	2/11		
>100	0	0	2/11		
Current age (years)	4.9 (3.0–9.5)	6.0 (2.0–8.0)	3.3 (0.3–9.5)	−0.1509	0.4347
Living in city	6/6	10/10	13/13	–	–
Having a hemophilia therapy center nearby	3/6	6/10	8/13	−0.0042	0.9828
Parent's highest level of education				−0.2432	0.2036
Bachelor	4/6	4/10	9/13		
Master	3/6	5/10	4/13		
Doctor of Philosophy	0	1/10	0		
With inhibitors	3/6	2/10	1/13	−0.3562	0.0579

Data are presented as *n*/*N* or median (range).
[a]Only 29 of 34 patients, participated in our study investigating the factors influencing regimen preferences. The others declined due to privacy concerns.
Abbreviations: CNY, Chinese yuan; EMI, emicizumab; –, not applicable.

TABLE 3 Bleeding events for previously untreated patients/minimally treated patients (PUP/MTP) versus previously treated patients (PTP)

Variables	PUP/MTP (*n* = 9)			PTP (*n* = 17)		
	During EMI	Before EMI	*P*	During EMI	Before EMI	*P*
ATBR[a]	0 (0–2)	2 (0–3)	0.0859	0 (0–0)	4 (0–18)	0.0001
ABR[b]	0 (0–4)	2 (0–3)	0.3714	0 (0–4)	4 (0–18)	<0.0001
ZBR[c] (%)	44.4	11.1	0.1144	76.5	11.8	0.0001

Data are presented as median (range).
[a]Collected for ≥ 6 months during EMI therapy versus ≥ 6 months before EMI therapy.
[b]Collected for ≥ 6 months during EMI therapy versus ≥ 6 months before EMI therapy.
[c]Collected for 12 months during EMI therapy versus ≥ 6 months before EMI therapy.
Abbreviations: ABR, annual bleeding rate; ATBR, annualized treated bleeding rate; EMI, emicizumab; MTP, minimally treated patients; PTP, previously treated patients; PUP, previously untreated patients; ZBR, zero bleeding rate.

Patients who were followed up for more than 6 months included nine (75.0%) of the 12 PUP/MTP patients and 17 (77.3%) of 22 PTP patients. Table 3 shows the median ATBR, ABR, and ZBR were similar during and before EMI among the nine PUP/MTP patients. On the contrary, among the 17 PTP patients, the ATBR and ABR during EMI therapy were significantly lower and ZBR significantly higher than before EMI.

Inhibitors versus non-inhibitors

Eight (23.5%) of the 34 patients had inhibitors, of whom seven (87.5%) were SHA. They started using EMI at 3.5 (1.6–9.1) years of age. Their 4-weekly maintenance dosage was 4.0 (1.6–6.0) mg/kg. Twenty-six (76.5%) patients did not have inhibitors, of whom 19 (73.0%) were SHA. When compared to the patients with inhibitors, patients without

TABLE 4 Bleeding events for patients with inhibitors versus without inhibitors

Variables	With inhibitors ($n = 5$)			Without inhibitors ($n = 21$)		
	During EMI	Before EMI	*P*	During EMI	Before EMI	*P*
ATBR[a]	0 (0–0)	7 (2–13)	0.0079	0 (0–2)	2 (0–18)	< 0.0001
ABR[b]	0 (0–4)	7 (2–13)	0.0238	0 (0–4)	2 (0–18)	0.0002
ZBR[c] (%)	60.0	0.0	0.0384	66.6	9.5	0.0001

Data are presented as median (range).
[a]Collected for ≥ 6 months during EMI therapy versus ≥ 6 months before EMI therapy.
[b]Collected for ≥ 6 months during EMI therapy versus ≥ 6 months before EMI therapy.
[c]Collected for 12 months during EMI therapy versus ≥ 6 months before EMI therapy.
Abbreviations: ABR, annual bleeding rate; ATBR, annualized treated bleeding rate; EMI, emicizumab; ZBR, zero bleeding rate.

inhibitors started using EMI at a significantly younger age, at 1.3 (0.1–6.6) years ($P = 0.0153$). Their 4-weekly EMI maintenance dosage was similar at 4.5 (3.6–6.3) mg/kg ($P = 0.0960$).

Patients who were followed up for more than 6 months included 5 (62.5%) of the 8 patients with inhibitors and 21 (80.8%) of 26 patients without inhibitors. Compared to the period before using EMI, their median ATBR and ABR during EMI therapy was significantly lower and their ZBR was significantly higher (Table 4).

Outcomes of various dosage-reduction during the maintenance period

Table S1 details the outcome of patients on different maintenance dosing regimens.

Patients who were followed up for more than 6 months included 26 (76.5%) of the 34 patients. Of the 26 patients, the 4-weekly EMI maintenance dosage was < 4.0 mg/kg in 8 (30.8%) patients, 4.0–5.0 mg/kg in 12 (46.1%) patients, and > 5.0 mg/kg in six (23.3%) patients. The detailed EMI concentration, equivalent FVIII activity, injection intervals, ATBR, ABR, and ZBR are all displayed in Table S1. In the follow-up records of all patients, regardless of the dosage used, their injection intervals were not significantly different ($P > 0.05$). The bleeding phenotype observed in bleeds requiring treatment was trauma-induced, with no instances of spontaneous bleeding. Moreover, the bleeding episodes were mild and limited to superficial muscles and soft tissues; there were no occurrences of joint bleeding or life-threatening hemorrhages. The bleeding phenotype for bleeds not requiring treatment included bruises and hematomas. After 6 months of EMI, we found no significant difference in ATBR and ABR between patients on different maintenance dosages ($P > 0.05$). However, the ZBR was significantly lower with maintenance dosages below 4 mg/kg ($P = 0.0156$).

Identification of optimal dosage thresholds

We used ROC curves, plotting ZBR independently against the 4-weekly maintenance dosage, the EMI concentration, and the FVIII-like activity, to provide threshold values above which ZBR could be maintained. The threshold values we obtained were: for 4-weekly EMI maintenance dosage, 3.8 mg/kg (Figure 3A); for EMI concentration, 48.1 μg/mL (Figure 3B); and for FVIII-like activity, 15.4 IU/dL (Figure 3C). By applying the bootstrap method with 1000 resamples across these variables, we calculated 95% confidence intervals for the area under curve scores, which resulted in 0.776–1.000 for the 4-weekly EMI maintenance dosage, 0.625–1.000 for the EMI concentration, and 0.758–1.000 for the FVIII-like activity.

DISCUSSION

Epidemiological overview and regimen preference

Currently, in China, hemophilia patients treated with EMI are predominantly young children with SHA without inhibitors. We are also seeing more PTP and MTP – currently representing 35% of patients with HA in our center which is an increase since our report two years ago.[3] EMI is expensive for our patients explaining why over 91% of patients in our center opted for reduced dosage.

Efficacy of reduced EMI dosage

Our study shows that even with reduced EMI dosage, excellent bleeding prevention could still be achieved. We found that all patients regardless of their inhibitor status, severity, and age experienced a marked decrease in ATBR and ABR and an increase in ZBR while taking EMI even with reduced maintenance dosage, compared to treatments they received before EMI. Our observation is consistent with the findings of other international studies, showing efficacy using reduced EMI dosage, including studies from India,[5] Malaysia,[6] Thailand,[7] and Finland.[8]

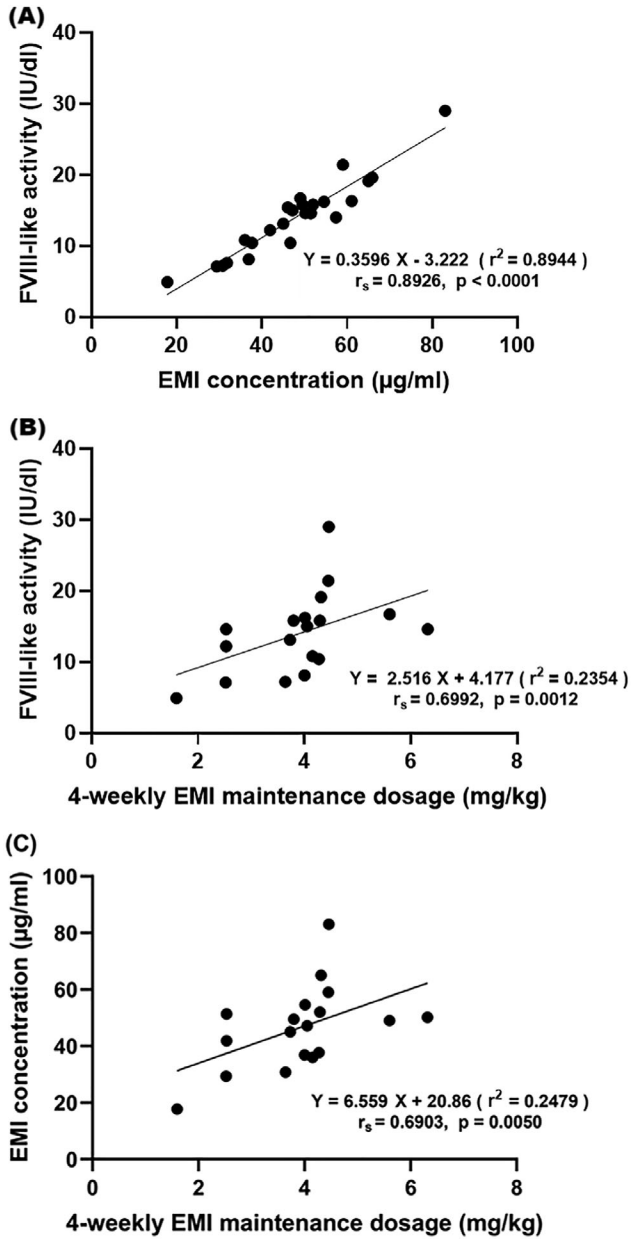

FIGURE 2 Correlation analysis of (A) EMI concentration and factor VIII (FVIII)-like activity (the 25 paired data points include seven from the loading period and 18 from the maintenance period), (B) 4-weekly EMI maintenance dosage and FVIII-like activity (the 18 paired data points from the maintenance period), and (C) EMI 4-weekly maintenance dosage and EMI concentration (the 18 paired data points from the maintenance period). EMI, emicizumab; r_s, Spearman correlation coefficient.

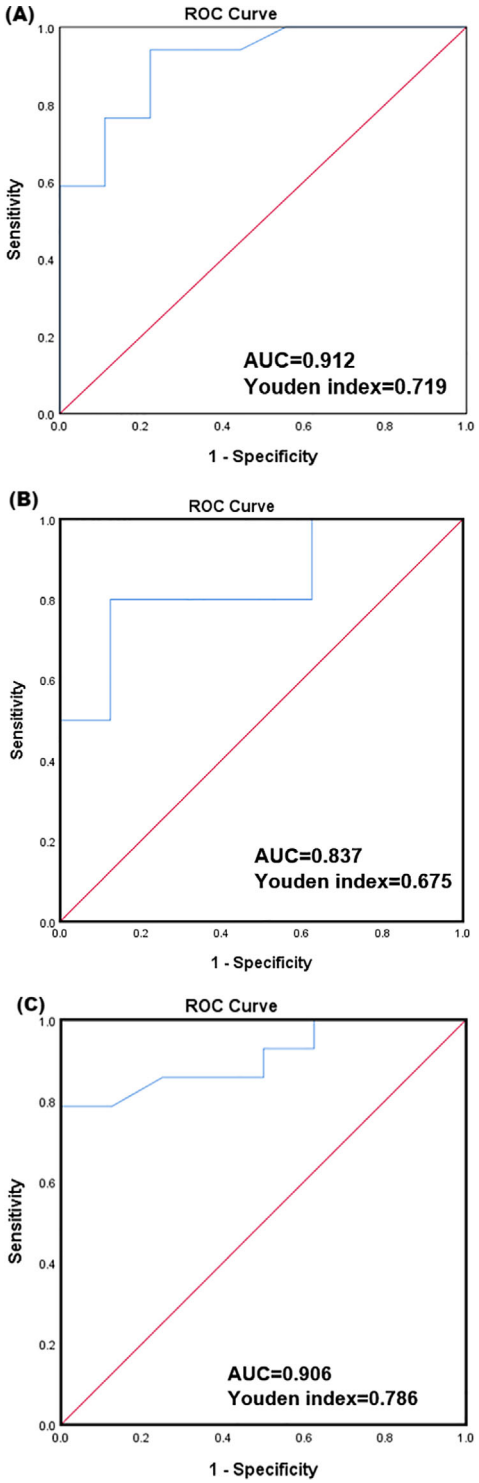

FIGURE 3 Receiver operator characteristic (ROC) curves illustrating (A) ZBR in relation to the 4-weekly EMI maintenance dosage. For EMI 4-weekly maintenance dosage, the threshold value at which ZBR could be maintained is 3.8 mg/kg. (B) ZBR in relation to EMI concentration. For EMI concentration, the threshold value at which ZBR could be maintained is 48.1 μg/mL. (C) ZBR in relation to factor VIII (FVIII)-like activity. For FVIII-like activity, the threshold value at which ZBR could be maintained is 15.4 IU/dL. EMI, emicizumab; ZBR, zero bleeding rate; AUC, area under the curve.

However, our study suggests that while reduced dosage effectively prevented bleeding, prolonged treatment at < 4 mg/kg every 4 weeks might increase the ABR and decrease ZBR (Table S1), particularly for untreated bleeding events such as subcutaneous bleeding, bruises, and hematomas. Our ROC plot of ZBR against the 4-weekly EMI maintenance dosage produced a maintenance dose

threshold value of 3.8 mg/kg (Figure 3A), below which the bleeding risk is predicted to increase.

Thus, we believe that for fixed-dose treatment, it is essential to ensure the 4-week maintenance dose is greater than 3.8 mg/kg although we need additional experience for validation. There are other studies using reduced 4-weekly maintenance doses based on clinical experience rather than ROC plots. These included 0.84–2.6 mg/kg for 8 cases in India,[5] 1.05–1.66 mg/kg for 6 cases in Thailand,[7] 1.7–1.9 mg/kg for 3 cases in Malaysia,[6] and 1.33–6 mg/kg for 11 cases in Finland.[8]

EMI pharmacokinetics and possibilities for dosage tailoring

In our Pharmacokinetics study, the good correlation between EMI concentration and FVIII-like activity is consistent with findings in other international studies during regular use of EMI.[9,10] As anticipated, we also found individual pharmacokinetic differences among different patients. For instance, Table 1 illustrates that at a consistent 4-week maintenance dosage of 2.5 mg/kg, the EMI concentration was 29.4 μg/mL for PN-02, 41.9 μg/mL for PN-05 and 51.4 μg/mL for PN-16, while the FVIII-like activity was 7.1 IU/dL for PN-02, 12.2 IU/dL for PN-05, and 14.6 IU/dL for PN-16. These findings highlight the importance of personalized treatment approaches to further improve the outcomes beyond fixed dosing.

Our study shows that evaluating therapeutic efficacy using EMI concentration and FVIII-like activity is both feasible and preferable and it is therefore possible to tailor the maintenance dosage by measuring either of these parameters. Our ROC plots showed a threshold for ZBR including an EMI concentration of 48.1 μg/mL (Figure 3B) and FVIII-like activity of 15.4 IU/dL (Figure 3C). Thus, instead of using a fixed EMI dose $>$ 3.8 mg/kg, a possibility is to measure plasma EMI concentration or FVIII-like activity to adjust the dosage to aim at values above the respective threshold.

The use of EMI pharmacokinetics to determine dosage has recently been advocated also by other studies.[11] The DosEmi study[11] suggested EMI dosing aimed at a trough EMI concentration of 30 μg/mL would be non-inferior to the standard dosing for preventing treated bleeds in HA patients. This threshold EMI concentration of 30 μg/mL was derived from phase I-III studies based on the non-inferiority of ATBR. Our threshold level of 48.1 μg/mL was higher, as it was based on ROC for ZBR, and was therefore aiming at zero bleed outcomes.

Among the two assessment methods, the FVIII-like activity measurement may be easier since ready-made test kits (Biophen Plasma Calibrator reagent) for FVIII-like activity measurement are already available. These measurements allow the accommodation of individual pharmacokinetic variations observed among patients taking EMI. Moreover, a refined dosage reduction plan towards individualized treatment can be accomplished by the incorporation of other patient factors such as bleeding phenotype, degree of arthropathy, musculoskeletal function, and the desired or required activity of the individual patients.

Our subsequent studies will aim to integrate the varying patient factors to better tailor treatments. Additionally, a topic of our growing interest is the impact of loading dosage: specifically, how the initial dosage might influence the efficacy in the maintenance phase. This is an area we'll delve into in upcoming research.

Limitations

A limitation of this study is the small sample size. In our study of 34 patients, the small sample size may pose challenges to the validity of the ROC analysis. To bolster the reliability of our findings despite the small sample size, we conducted additional statistical analysis using the bootstrap method with 1000 resamples. The results across the board reinforce the credibility of the ROC analysis: The EMI maintenance dosage, EMI concentration, and FVIII-like activity all showed 95% confidence intervals of 0.776–1.000, 0.625–1.000, and 0.758–1.000, respectively. Although these wide ranges suggest a degree of uncertainty, they also indicate that the maintenance dosage, EMI concentration, and FVIII-like activity are reliable predictors of zero-bleeding, demonstrating the clinical utility of the ROC analysis. Another limitation of this study is its real-world nature, where patients did not strictly adhere to the QW, Q2W, or Q4W injection regimen. Instead, the dosing intervals were adjusted according to individual patient needs or circumstances. Thus, a limitation of this study is its inability to determine if a similar threshold of reduced dosage, if applied using the standard QW, Q2W, or Q4W regimen, would yield comparable results. Previous studies have shown that the distribution of peaks and troughs in EMI concentration widens as the dosing interval increases.[9,12] However, no studies have yet demonstrated that for the standard 4-weekly maintenance dosage of 6 mg/kg, the choice of a QW, Q2W, or Q4W injection regimen impacts the effectiveness in controlling bleeding. Despite these limitations, our study did demonstrate that reducing EMI dosage without compromising outcomes can be rationally performed. This will be the preliminary step towards tailoring EMI dosage for individualized treatment.

Conclusion

Our study confirms the effectiveness of prophylactic EMI treatment at a lower-than-recommended dosage for

children with HA in China. We propose that our findings suggest the possibility of reducing EMI dosage in a rational and objective manner without necessarily compromising outcomes, although further research is needed to definitively establish this. Rational dose reduction is particularly important and cost-effective for patients in countries with economic constraints, such as China. Future studies will aim to explore how individualization of maintenance EMI dosage could be accomplished by the incorporation of individual patient factors.

CONFLICT OF INTEREST

Man-Chiu Poon has received grant funding from Bayer and CSL-Behring; attended advisory board meetings of Bayer, CSL-Behring, KVR Pharma, Novo Nordisk, Octapharma, Pfizer, Roche, SOBI, and Takeda. Other authors stated that they had no conflicts of interest or bias.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Mao Q, Chen Z, Liu G, Li G, Zhen Y, Cheng X, et al. Real-world use of emicizumab in Chinese children with hemophilia A: Retrospective data from a comprehensive care center. *Pediatr Investig*. 2024;8:244–252. https://doi.org/10.1002/ped4.12439