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LETTER TO THE EDITOR

Real-world data for the use of emicizumab in haemophilia A patients with inhibitors – First nationwide report from Korea

Emicizumab is the first nonfactor drug developed and approved for patients with haemophilia A (PwHA) that mimics the activity of FVIII. Emicizumab has shown excellent bleeding prevention results in clinical trials (e.g., HAVEN 1), and was first approved in the USA for PwHA with inhibitors (PwHAi) in November 2017, followed by approval in Europe and Japan.[1] Subsequent clinical trials (HAVEN 2–4) have shown the efficacy of emicizumab in PwHA with inhibitors (PwHAi) and without inhibitors. The recent World Federation of Haemophilia guideline strongly recommends using emicizumab for PwHAi.[2] Since its release, there has been an expectation that emicizumab, with its higher efficacy and convenient subcutaneous administration, would improve many of the unmet needs of care in haemophilia patients. As expected, long-term and real-world data using emicizumab have started to show that emicizumab is safe and effective for PwHA. Nevertheless, due to its later approval in Asia, there is limited experience with emicizumab in Asian populations. The phase 3 HAVEN 5 clinical trial in the Asia-Pacific region recently reported that emicizumab prophylaxis is as effective as that shown in previous reports.[3] In Korea, emicizumab has been marketed since January 2019, receiving national insurance reimbursement in May 2020 for PwHAi. Herein, we describe the first real-world analysis of emicizumab use in Korean PwHAi.

The study was conducted from March 2021 to October 2022 at five centres in Korea which treat PwHAi. All patients in Korea who had experience of using emicizumab for more than 6 months were included in the study. One patient who participated in the HAVEN study, and used emicizumab before the market release in Korea, was included. After study enrolment, patients' data were collected both retrospectively and prospectively, including patients' demographic characteristics, bleeding patterns 6 months before and after using emicizumab, inhibitor titres and emicizumab concentrations while prescribing the drug. Inhibitor titres were measured using the FVIII chromogenic assay with bovine reagents after emicizumab use. Annualised bleeding rate (ABR) was estimated according to the duration. Data cut-off date was 31 October 2022.

The study included a total of 16 PwHAi (seven paediatric patients and nine adults [aged > 19 years]; Table 1) with a median age of 20.9 years (range 1.4–48.3). There was no difference between the highest historical inhibitor titres among the age group. Before emicizumab prophylaxis, most patients were using bypassing agent prophylaxis: activated prothrombin complex concentrate (aPCC) in seven patients, four using activated recombinant FVII (rFVIIa), and one patient using both. One patient was undergoing immune tolerance induction (ITI) therapy using high dose (50 IU/kg three times a week) plasma-derived FVIII. Two patients were receiving on-demand treatment, while one patient changed to emicizumab from fitusiran (Table S1). The estimated mean ABR of all patients was 14.1 (SD ± 14.2). The ABR of the adult group appeared higher than that in the paediatric group (median 14.0 vs. 7.0) but there was no statistical difference in bleeding rate between the two groups before emicizumab use. For the paediatric group, the time period between inhibitor development and the start of emicizumab use was shorter (median 2.9 years) compared to the adult group (median 25.9 years). The median duration of emicizumab use was 717.5 days (range 369–1788 days) in all patients. Seven patients experienced dosing interval switching during emicizumab maintenance therapy, mainly due to compliance issues. These individuals changed dosing interval from once-weekly infusion to every other week or once-monthly infusion (Table S2). The remaining patients had unchanged dosing intervals: every week, every other week or every month, according to their lifestyle. After emicizumab use, zero bleeding was achieved in nine patients (56.3%), and ABR was decreased in all patients (median 0 [range 0–1.47], mean 0.35 [SD ± 0.49]) (Figure 1). Annualised joint bleeding was median 0 (range 0–1.24), mean 0.11 (SD ± 0.32) in all patients. Among the 16 patients, one patient had two major surgeries and one patient underwent a minor operation. Major surgery was performed with three additional doses of rFVIIa for each surgery; the minor surgery was conducted without any additional replacement therapy except for emicizumab (Table S2). Inhibitor titre after emicizumab use showed a decreasing tendency in 11 (73.3%) patients, while in four patients, the inhibitor titre increased (Figure S1). Median inhibitor titre decreased from 25.6 to 1.9 BU (range 0–419.4) after emicizumab prophylaxis, although there was no significant trend of change among the values. None of the patients who were able to be followed up for inhibitor change ($n = 15$) were exposed to FVIII during emicizumab use. The median emicizumab concentration for all 16 patients, measured at various time points, was 51.45 μg/mL (range 22.3–94.7) (Figure S2). There were no reported drug-related adverse events.

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TABLE 1 Patients' treatment history and Emicizumab use outcome.

	Paediatric patients	Adult patients*	All patients	*p* value
Total number of patients, *n* (%)	7 (43.7)	9 (56.3)	16	
Age at the start of emicizumab (years), median (range)	3.2 (1.4–14.0)	28.9 (20.6–48.3)	20.9 (1.4–48.3)	.002
Known highest inhibitor titre (BU), median (range)	26.7 (9.2–300)	22.8 (7.7–227.2)	24.2 (7.7–300)	.91
Treatment before emicizumab, *n* (%)				.32
aPCC	3 (42.8)	2 (22.2)	5 (31.3)	
rFVIIa	0	5 (55.6)	5 (31.3)	
aPCC or rFVIIa	3 (42.8)	1 (11.1)	4 (25.0)	
FVIII	1 (14.3)	0	1 (6.2)	
Fitusiran	0	1 (11.1)	1 (6.2)	
Inhibitor titre just before emicizumab start, median (range)	26.7 (0.5–300)	22.8 (13.8–227.2)	24.2 (0.5–300)	.45
ABR before emicizumab use, median (range)				.46
Median	7.0 (2–12)	14.0 (0–48)	10.5 (0–48)	
mean (± SD)	7.4 (± 3.7)	19.3 (± 17.3)	14.1 (± 14.2)	
Time since inhibitor development to emicizumab use (years), median (range)	2.9 (0.3–10.8)	25.9 (0.9–42.8)	9.6 (0.3–42.8)	.03
Duration of emicizumab use (days), median (range)	827 (369–1045)	589 (468–1788)	717.5 (369–1788)	.53
ABR after emicizumab use				.89
median (range)	0.35 (0.00–0.99)	0.00 (0.00–1.47)	0.00 (0.00–1.47)	
mean (± SD)	0.33 (± 0.37)	0.37 (± 0.60)	0.35 (± 0.49)	
AJBR after emicizumab use				.89
median (range)	0.00 (0.00–0.35)	0.00 (0.00–1.24)	0.00 (0.00–1.24)	
mean (± SD)	0.05 (± 0.13)	0.16 (± 0.41)	0.11 (± 0.32)	
Zero bleeding, *n* (%)	3 (42.9)	6 (66.6)	9 (56.3)	.62
Inhibitor titre after emicizumab use (BU)**, median (range)	3.85 (0.5–419.4)	1.0 (0–286.6)	2.6 (0–419.4)	.28

Abbreviations: ABR, estimated annualised bleeding rate; AJBR, estimated annualised joint bleeding rate; aPCC, activated prothrombin complex concentrate; BU, Bethesda unit; ITI, immune tolerance induction; rFVIIa, activated recombinant factor VII; SD, standard deviation.
*Adult patients (aged > 19 years).
**Except for one paediatric patient missing data.

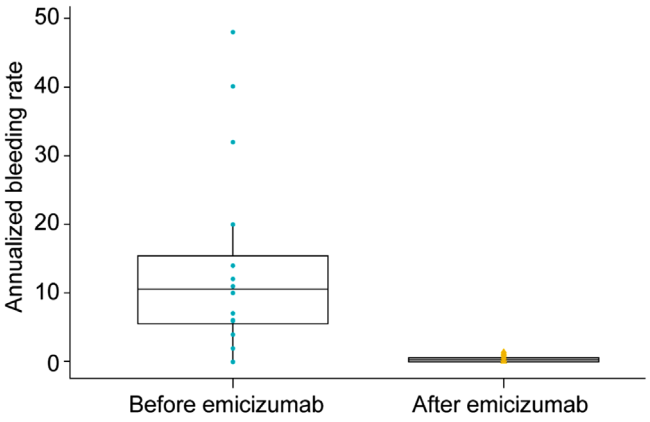

FIGURE 1 Comparison of annualised bleeding rate before and after emicizumab use ($p < .001$).

In this first real-world study in Korea of the use of emicizumab in PwHAi who had mostly been heavy bleeders with previous therapies, we observed very low ABR (mean 0.35 ± 0.49) and 56% of patients showed no bleeding events at all. Emicizumab demonstrated similar efficacy in adult and paediatric patients. All 16 patients had less than 1.5 ABR using emicizumab with various dosing schedules.

Long-term outcomes from the HAVEN studies showed that, among a total of 401 patients, emicizumab showed consistent bleeding control across a median of 120.4 weeks with a favourable safety profile.[4] The multicentre phase 3b STASEY study of once-weekly emicizumab prophylaxis in PwHAi aged > 12 years, analysed data from 193 patients over a median of 103.1 weeks.[5] In the STASEY study, zero bleeding was achieved in 82.6% of individuals, with a mean ABR of 0.6 (0.00–4.85). Although our data are derived from a small number of subjects compared to those studies, similar results were obtained after a median of 102.5 weeks of emicizumab exposure, with no reported drug-related adverse events. Our study highlights the application of drugs in the real-world and the results of our study can be considered important, especially consid-

ering that there are not many long-term data among children with inhibitors.

In the real-world setting, patients used different emicizumab dosing schedules according to personal circumstances or their physician's recommendation considering each patient's tolerability profile. Overall, 43.5% of individuals had longer dosing intervals with no increase in bleeding pattern. The once-monthly schedule was preferred for some patients, including children, due to the convenience of only visiting hospital once a month. Once-monthly dosing resulted in a slightly higher ABR in HAVEN 2 with 10 paediatric patients, and in HAVEN 4 with 41 patients aged ≥12 years.[6,7] Two paediatric patients in our study showed no bleeding with more than a year's duration of once-monthly emicizumab dosing. Although this is only a small number of patients, this demonstrates the possibility for the once-monthly regimen to be applicable to children in real-world settings.

Clinical experience of emicizumab use during surgical procedures has been reported to be mostly tolerable with minimal bleeding events or intervention, no discontinuation of drugs, and no thromboembolic events or deaths.[8,9] In our study, two patients underwent surgery: one patient had two major operations (right ankle arthroplasty, debridement; retroperitoneal mass excision, inguinal hernioplasty), with the second patient undergoing port removal. Patients who underwent major surgery used three doses of rFVIIa for post-operative bleeding control, whereas port removal required no additional factor replacement therapy. Our study confirms that the use of emicizumab made the surgical procedure easier and less burdensome for both healthcare providers and patients.

A few studies have reported a trend towards reduced inhibitor titres after emicizumab use in PwHAi.[1,10] We observed a decreasing tendency of inhibitor titres in most patients (11, 73.3%) and FVIII inhibitors disappeared in four patients. In contrast, four patients with higher inhibitor titres had increased inhibitor titres after emicizumab use. Changes in inhibitor titre with emicizumab use is an ongoing investigational matter; we were not able to analyse the underlying mechanism of these variations. It is recommended to measure FVIII inhibitor titre regularly in patients receiving emicizumab treatment.

Emicizumab concentrations across all patients were measured a total of 35 times during the study period, ranging from 1 to 4 times per patient. Although emicizumab concentrations were variable between patients, the mean emicizumab concentration was similar (53.08 μg/mL ± 19.84) to those reported in previous studies and showed stability with emicizumab use.[5,7]

There are several limitations associated with our study. This was a small study with a short observation period and no control group; moreover, patient monitoring or follow-up schedules were decided differently according to each investigator's choice. Hence, it was difficult to collect uniform data for laboratory results. The retrospective review of some patient data represents another limitation because it precluded the ability to compare subjective or objective improvements in joint health or patient quality of life (QoL).

Despite the limitations, our real-world Korean data demonstrate that emicizumab is an effective and safe treatment for both paediatric and adult PwHAi. In the real-world setting, PwHAi who were treated with emicizumab had a dramatic and stable decrease in ABR and improved QoL without significant side effects.

AUTHOR CONTRIBUTIONS

Seung Min Hahn wrote the documents to obtain ethics review board approvals, collected, interpreted, and analyzed the data, wrote the initial and final manuscript draft. Jung Woo Han, Jin Seok Kim, Ye Jee Shim, Soyon Kim, Hugh Chul Kim, and Young Shil Park contributed to data collection. Young Shil Park and Chuhl Joo Lyu conceptualized the study. All authors contributed to manuscript revisions and approved the final version of the manuscript as submitted.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest relevant to this article to disclose.

ETHICS STATEMENT

The study was approved by the institutional review board at each hospital (Severance Hospital IRB 2021-4102-001) in concordance with the Declaration of Helsinki. Informed consent was obtained from adult patients, and the parents of paediatric participants.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017;377(9):809-818.
2. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26(6):1-158.
3. Yang R, Wang S, Wang X, et al. Prophylactic emicizumab for hemophilia A in the Asia-Pacific region: a randomized study (HAVEN 5). *Res Pract Thromb Haemost*. 2022;6(2):e12670.
4. Callaghan MU, Negrier C, Paz-Priel I, et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies. *Blood*. 2021;137(16):2231-2242.
5. Jiménez-Yuste V, Peyvandi F, Klamroth R, et al. Safety and efficacy of long-term emicizumab prophylaxis in hemophilia A with factor VIII inhibitors: a phase 3b, multicenter, single-arm study (STASEY). *Res Pract Thromb Haemost*. 2022;6(8):e12837.
6. Young G, Liesner R, Chang T, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. *Blood*. 2019;134(24):2127-2138.
7. Pipe SW, Shima M, Lehle M, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. *Lancet Haematol*. 2019;6(6):e295-e305.
8. McCary I, Guelcher C, Kuhn J, et al. Real-world use of emicizumab in patients with haemophilia A: bleeding outcomes and surgical procedures. *Haemophilia*. 2020;26(4):631-636.
9. Cohen CT, Diaz R. Emicizumab in pediatric hemophilia: bleeding and surgical outcomes from a single-center retrospective study. *Pediatr Blood Cancer*. 2021;68(11):e29325.
10. Liu G, Huang K, Li G, et al. Real-world experience of emicizumab prophylaxis in young children with hemophilia A: retrospective data from China. *Front Pediatr*. 2022;10:992267.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.