

Real-world data on the use of emicizumab in patients with haemophilia A with and without inhibitors in Singapore

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ABSTRACT

Introduction: Emicizumab is a bispecific monoclonal antibody that mimics the function of factor VIII by binding to factor IXa and factor X to achieve haemostasis in haemophilia A. The long half-life and subcutaneous mode of administration makes emicizumab a compelling treatment option for bleeding prophylaxis. There is still limited real-world data on its use and management considerations, especially during surgical procedures. The objective of the study is to describe the real-world experience of emicizumab in a cohort of adult and paediatric haemophilia A patients in Singapore, including its use in the periprocedural setting.

Method: This was an observational study conducted at the 2 main haemophilia treatment centres in Singapore. All haemophilia A patients who commenced treatment with emicizumab before 1 July 2022 were recruited.

Results: A total of 18 patients with haemophilia A were included in this study. Ten (55.6%) patients had active inhibitors. The median annual bleeding rate for all patients before emicizumab use was 4.5 events (interquartile range [IQR] 2.8–8.3) compared with 0 events (IQR 0–0) after emicizumab was commenced ($P=0$). There were no adverse events of venous or arterial thrombosis, thrombotic microangiopathy, or death. A total of 6 procedures in 5 patients were performed during the study period with no major bleeding complications.

Conclusion: Emicizumab effectively protects against bleeding in haemophilia A patients with and without inhibitors, including in children less than 12 years old. More studies are required to address clinical nuances, such as periprocedural management and the role of immune tolerance in patients with inhibitors on emicizumab.

Ann Acad Med Singap 2023;52:580-9

Keywords: emicizumab, haemophilia A, haemostatic agent, inhibitor, prophylaxis

CLINICAL IMPACT

What is New

- This study adds real-world data on the effectiveness of emicizumab in protecting haemophilia A patients with and without inhibitors, including in children less than 12 years old, against bleeding.

Clinical Implication

- This data can guide policymaking to improve the accessibility of this effective but costly treatment option to haemophilia A patients in Singapore.

which results in a deficiency of factor VIII (FVIII).¹ The mainstay of treatment is FVIII replacement, which can be administered as prophylaxis or on-demand.² While FVIII replacement has greatly improved outcomes in people with haemophilia A, they still face multiple challenges.

The most serious complication of haemophilia A management is the development of inhibitors, which are alloantibodies directed against infused factors. Individuals who develop inhibitors will not be able to use FVIII replacement for the treatment of bleeding or for prophylaxis, and have an increased risk of bleeding.³ For patients without inhibitors, the high frequency of intravenous administration of FVIII, usually 3 times a week, results in problems with venous access and need for indwelling catheters.^{4,5} Extended half-life products can decrease the frequency of FVIII administration; however, the reduction may be modest.⁶ Novel agents for the treatment of haemophilia A are required to address these issues.

Emicizumab is a bispecific monoclonal antibody that mimics the function of FVIII by binding to factor IXa and factor X to achieve haemostasis

INTRODUCTION

Haemophilia A is an X-linked hereditary bleeding disorder caused by pathogenic genetic variants,

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in haemophilia A.⁷ Initial trials demonstrated impressive efficacy in preventing bleeding episodes in patients with haemophilia A with inhibitors, both in the adult and paediatric population.^{7,8} Similar results were seen in patients with haemophilia A without inhibitors.^{9,10} This enabled regulatory approval for routine prophylaxis to prevent or reduce bleeding episodes in patients with haemophilia A with or without FVIII inhibitors of all age groups.^{11,12}

Emicizumab is an alternative treatment option for people with haemophilia A. It serves the unmet need of providing prophylaxis against bleeds in patients with inhibitors and enables treatment at a lower frequency and via an easier route of administration for those without inhibitors. Yet, more data are required to demonstrate the efficacy, safety profile and nuances around the use of emicizumab in the real-world setting. This is especially so in the periprocedural setting, where there is much more heterogeneity in management.

Singapore is a small island nation in the Asia-Pacific with a small but high-needs haemophilia population with a prevalence of 10.31 per 100,000 males, with an inhibitor rate of 17.9%.¹³

The recent HAVEN 5 study evaluated prophylactic emicizumab for haemophilia A in the Asia-Pacific region in a randomised controlled study.¹⁴ This provides very limited data from the Asia-Pacific region. In this study, we describe real-world data on the use of emicizumab in Singapore in paediatric and adult populations.

METHOD

This was an observational study conducted at 3 public hospitals in Singapore—Singapore General Hospital (SGH) and KK Women's and Children's Hospital (KKH). The study received Institutional Review Board approval from both centres. SGH is the largest adult tertiary hospital in Singapore, and adults with haemophilia A were recruited from the centre, while KKH is the largest paediatric hospital in Singapore, and children with haemophilia A were recruited from this centre. Data collection was performed retrospectively from the Blood Disorder Registry at SGH and from the Bleeding Disorders Registry at KKH. Data were analysed in July 2022. Emicizumab was first used in September 2020 at SGH and in September 2018 at KKH. All haemophilia A patients who commenced emicizumab before 1 July 2022 were included in the study.

Data collection included demographics, baseline haemophilia A history (inhibitor, prophylaxis, immune tolerance induction [ITI], bleeding events) 1 year before emicizumab initiation and post-emicizumab data (emicizumab dosing regime,

inhibitor, concurrent prophylaxis or ITI, bleeding events, side effects) 1 year after emicizumab initiation. Patients' minor bleeding episodes were recorded by the patients or caregivers, and documented in the electronic medical records during clinic visits, while more severe bleeding episodes were reviewed by our specialty nurses or haematologists before getting documented in the electronic medical records. Stable patients were reviewed in clinics every 6 months. Patients with higher frequency of bleeds were reviewed more frequently. Annualised bleeding rates (ABRs) were calculated to account for variable follow-up periods. Data were collected from patients undergoing invasive procedures, including procedure type, products used before and after procedures, and bleeding or thrombotic complications during or after surgery. Monitoring of FVIII replacement and inhibitor titres were performed by a bovine-based FVIII chromogenic assay while patients were on emicizumab.

Group comparisons between patients with and without inhibitors were performed with Mann-Whitney U test and Fisher's Exact test. Bleeding data (median ABR, proportion of patients with 0 bleeding events, and proportion of patients with target joints) pre- and post-emicizumab were compared using Wilcoxon sign-rank test and McNemar test. A *P* value of <0.05 was considered statistically significant. The bleeding outcomes for patients less than 12 years old were analysed as a separate cohort. Statistical analysis was performed using SPSS version 20.0 software (SPSS Inc, Chicago, IL, US).

RESULTS

Eighteen patients were included in the analysis. Their demographic data are presented in Table 1. The median age at the initiation of emicizumab was 6.3 years old (range: 0.08–49.0)—15 were children with a median age of 5 years (range: 0.08–17.5), while 3 patients were adults with a median age of 43 years (range: 21.0–49.0). The median duration of emicizumab prophylaxis was 21.5 months (range: 3.0–46.0). All except 1 patient was male, and 16 (88.9%) patients had severe haemophilia A. Twelve (66.7%) patients were on prophylaxis before emicizumab initiation, with 11 receiving factor VIII prophylaxis and 1 receiving recombinant activated factor VII (rFVIIa) prophylaxis. Ten (55.6%) patients had active inhibitors before initiating emicizumab. Among the patients with active inhibitors, the median inhibitor titre before emicizumab initiation was 9.3 BU (interquartile range [IQR] 6.52–21.3 BU) and all had high-responding inhibitors. Three (37.5%) patients were receiving ITI before emicizumab initiation.

The 2 most common indications for initiating emicizumab prophylaxis were the presence of inhibitors (8 patients) and frequent bleeds

in haemophilia A patients without inhibitors (6 patients). Patients were switched from FVIII prophylaxis if the ABR was 2 or more while on FVIII

Table 1. Demographics.

Characteristics	Patients with no inhibitors (n=10)	Patients with inhibitors (n=8)	P value
Median age of starting emicizumab (IQR), years	7.9 (2–16.1)	4.1 (1.9–35.5)	0.929
0 to <2 years, no. (%)	2 (20)	2 (25)	
2 to <6 years, no. (%)	2 (20)	3 (37.5)	
6 to <12 years, no. (%)	3 (30)	0 (0)	
12 to <18 years, no. (%)	2 (20)	1 (12.5)	
>18 years, no. (%)	1 (10)	2 (25)	
Sex, no. (%)			
Male	10 (100)	7 (87.5)	0.444
Race, no. (%)			
Chinese	4 (40)	7 (87.5)	0.199
Malay	3 (30)	1 (12.5)	
Indian	1 (10)	0 (0)	
Others	2 (20)	0 (0)	
Severity, no. (%)			
Mild	0 (0)	1 (12.5)	0.245
Moderate	0 (0)	1 (12.5)	
Severe	10 (100)	6 (75)	
Reason for switching to emicizumab, no. (%)			
Inhibitor	0 (0)	8 (100)	NA
Frequent bleed	6 (60)	0 (0)	
Venous access issues	3 (30)	0 (0)	
Parental/patient request	1 (10)	0 (0)	
Pre-emicizumab			
Prophylaxis prior to emicizumab, no. (%)			
FVIII	8 (80)	2 (25)	0.057
rFVIIa	0 (0)	1 (12.5)	
On demand therapy	2 (20)	5 (62.5)	
ITI before emicizumab, no. (%)	NA	3 (37.5)	NA
Median exposure days to FVIII (IQR) at the onset of inhibitors	NA	24 (10–39) ^a	NA
Median inhibitor titres before emicizumab, BU, years (IQR)	NA	9.3 (6.5–21.3)	NA
High-responding inhibitor, no. (%)	NA	8 (100)	NA
Post-emicizumab			
Median duration of emicizumab, months (IQR)	22 (7.0–32.5)	21 (10.5–23.3)	0.562
Median exposure days (IQR) to emicizumab	38 (23.3–51.3)	41 (11.5–66.8)	0.859

Table 1. Demographics. (Cont'd)

Characteristics	Patients with no inhibitors (n=10)	Patients with inhibitors (n=8)	P value
Emicizumab regime, no. (%)			
Weekly	0 (0)	1 (12.5)	0.331
2-weekly	7 (70)	3 (37.5)	
3-weekly	0 (0)	1 (12.5)	
4-weekly	3 (30)	3 (37.5)	
Concurrent FVIII with emicizumab, no. (%)			
Currently ongoing	1 (10)	NA	NA
Never had	4 (40)		
Previously had	5 (50)		
Concurrent ITI with emicizumab, no. (%)			
Currently ongoing	NA	6 (75)	NA
Never had		1 (12.5)	
Previously had		1 (12.5)	
Median latest inhibitor titre (IQR), BU	0 (0) ^b	5.2 (0.4–57.5)	NA

FVIII: factor VIII; ITI: immune tolerance induction; IQR: interquartile range; NA: not applicable; rFVIIa: recombinant activated factor VII
^a n=7; 1 missing value as 1 patient had developed inhibitors more than 30 years ago, the exposure days to FVIII could not be determined.

^b n=8; 2 missing values as 2 patients had not had inhibitors checked since starting emicizumab.

prophylaxis. The 5 patients without inhibitors, who were switched to emicizumab, had ABRs ranging from 2 to 14. The 1 patient without inhibitors, who was started on emicizumab without prior FVIII prophylaxis, was a 4-week-old neonate who had 2 episodes of subdural haemorrhage. All patients were started on the initiation regime of emicizumab 3 mg/kg once weekly for 4 weeks. In the paediatric population, 10/15 (66.7%) were on a 2-weekly 3 mg/kg regime, 1 was on a weekly 1.5 mg/kg regime and 1 was on a 3-weekly 4.5 mg/kg regime, while all adult patients were on a 4-weekly 6 mg/kg regime. Given the wide range of body weights in the paediatric subgroup and the standardised dosing in each vial of emicizumab, different frequencies of emicizumab administration are required to achieve the most cost-effective use of emicizumab in this subgroup. Only 1 patient had ongoing concurrent FVIII administration among patients with no inhibitors. Most patients (n=6) with inhibitors had ongoing ITI with emicizumab prophylaxis.

Bleeding outcomes

The median ABR for all the patients before emicizumab prophylaxis was 4.5 events (IQR 2.8–8.3) compared to 0 events (IQR 0–0) after

emicizumab was commenced ($P=0.000$) (Table 2). When stratified into patients with and without inhibitors, the improvement in median ABR after commencing emicizumab remained statistically significant for both groups. The median ABR in patients without inhibitors prior to emicizumab was 3.0 events (IQR 0.8–10.3) compared with 0 events (IQR 0–0) on emicizumab ($P=0.012$). In patients without inhibitors, the median ABR prior to emicizumab was 5.5 events (IQR 4.0–8.0) compared with 0 events (IQR 0–2.3) on emicizumab ($P=0.011$).

There was a higher proportion of patients with 0 bleeding events in the first 6 months after commencing emicizumab compared to the 6 months before commencing emicizumab (83.3% versus 22.2%, $P=0.001$) (Table 2). When stratified into patients with and without inhibitors, the increase in proportion of patients with 0 bleeds after commencing emicizumab was seen in both groups but only remained statistically significant in patients without inhibitors (non-inhibitor group: from 30% to 90%, $P=0.031$; inhibitor group: from 12.5% to 75%, $P=0.063$). There was no statistically significant difference in the proportion of patients with target joints before and after the commencement of emicizumab.

We performed a separate analysis on the bleeding outcomes in patients under 12 years old because this age cohort has the least published data (Table 3). There were 12 patients in this age group, with 5 having active inhibitors. Similar to the overall analysis, the median ABR was lower (4 events lowered to 0 events, $P=0.003$), and the proportion of patients with 0 bleeding events was higher (8.3% increased to 91.7%, $P=0.002$) after the commencement of emicizumab. A similar trend was preserved when stratified into patients with and without inhibitors.

Four children were initiated on emicizumab when they were less than 2 years old, and 2 of them had active inhibitors (Table 3). The other 2 children had no inhibitors and were started on emicizumab prophylaxis after spontaneous intracranial haemorrhage events. All had improved ABR (median ABR improved from 4 pre-emicizumab to 0 post-emicizumab), and 3 had 0 bleeding events after emicizumab commencement.

Of the 10 patients without inhibitors, only 1 had emicizumab commenced before 50 exposure days (EDs) to FVIII. Emicizumab was initiated at 12 EDs to FVIII when the patient was 4 weeks old. FVIII administration was continued once a week until 25 EDs and inhibitors to FVIII were monitored regularly. No inhibitors to FVIII were detected during the period of follow-up.

Procedural outcomes

A total of 6 procedures in 5 patients were performed during the study period (Table 4). All except 1 were minor procedures (3 port removals, 1 wisdom tooth extraction, 1 circumcision). There were 2 procedures done on the same patient with active inhibitor for which periprocedural rFVIIa was given. The remaining procedures were done in patients with no active inhibitors, and periprocedural FVIII replacement was given. There were no significant bleeding or thrombotic events documented.

Concurrent ITI with emicizumab prophylaxis

There were 7 patients who were on concurrent ITI therapy and emicizumab (Table 5). Four patients had ITI therapy prior to the initiation of emicizumab, the other 3 were started on ITI while on emicizumab. Low-dose ITI regimes were started for most patients. We had 1 case where a low-dose regime (50 IU/kg every other day [EOD]) was stepped up to a higher dose regime (150 IU/kg EOD) in light of bleeding manifestations. Emicizumab was started after the step-up, and the ITI dosing was decreased back to a low-dose regime after bleeding symptoms improved. Three out of 7

patients achieved eradication of inhibitor while on concurrent therapy.

Safety

None of the 18 patients discontinued emicizumab. They were not screened for anti-emicizumab drug antibodies as per standard clinical practice. There was no loss of clinical efficacy to emicizumab as a clinical surrogate. There was also no patient who developed inhibitors to FVIII while receiving emicizumab. There were no adverse events of venous or arterial thrombosis, thrombotic microangiopathy or death.

DISCUSSION

Our study has demonstrated similar effectiveness of emicizumab in people with haemophilia A to those reported in clinical trials.¹⁵ Patients with and without inhibitors experienced an improvement in median ABR after the commencement of emicizumab. Both groups in our study had an increase in the proportion of patients with 0 bleeding events over 6 months after the commencement of emicizumab. Although the difference was not clinically significant in the inhibitor group, it is likely due to the small sample size.

The efficacy and safety of emicizumab across a broad population of adults with haemophilia A, with or without FVIII inhibitors, have been demonstrated in the HAVEN clinical trials: HAVEN 1 (NCT02622321), HAVEN 3 (NCT02847637) and HAVEN 4 (NCT03020160).⁷⁻¹⁰ Only the HAVEN 2 (NCT02795767) trial investigated emicizumab prophylaxis in children below 12 years old with haemophilia A but was limited to children with inhibitors.⁸ Of the 88 children recruited, only 8 children were less than 2 years old. Published data on the safety and efficacy of emicizumab prophylaxis among paediatric patients with no inhibitors and in the infant/toddler group are still limited.

The HOHOEMI study reported good clinical efficacy of emicizumab in 13 paediatric severe haemophilia A patients without inhibitors.¹⁶ In this study, only 3 out of 13 children were aged less than 2 years. Barg et al. described a cohort of 40 paediatric previously treated patients, of whom 18 had inhibitors, and 22 had no inhibitors (9 children were less than 1 year old) with a low ABR and no safety concerns after commencing emicizumab.¹⁷ In another study by Barg et al., they described the effective use of emicizumab prophylaxis in reducing bleeds in 11 infants and toddlers with inhibitors (7 were under the age of 2 years).¹⁸ McCary et al. reported on a cohort of 49 previously treated

Table 2. Overall bleeding data.

Bleeding data	All patients (n=18)			Patients without inhibitors (n=10)			Patients with inhibitors (n=8)		
	Pre-emicizumab	Post-emicizumab	P value	Pre-emicizumab	Post-emicizumab	P value	Pre-emicizumab	Post-emicizumab	P value
Median ABR (IQR)	4.5 (2.8–8.3)	0 (0)	0.000	3 (0.8–10.3)	0 (0)	0.012	5.5 (4–8)	0 (0–0.8)	0.011
Zero bleeding events in 6 months, no. (%)	4 (22.2)	15 (83.3)	0.001	3 (30)	9 (90)	0.031	1 (12.5)	6 (75)	0.063
Presence of target joint, no. (%)	2 (11.1)	0 (0)	0.500	1 (10)	0 (0)	1.000	1 (12.5)	0 (0)	1.000
Subpopulation: Children less than 12 years old									
	All patients (n=12)			Patients without inhibitors (n=7)			Patients with inhibitors (n=5)		
	Pre-emicizumab	Post-emicizumab	P value	Pre-emicizumab	Post-emicizumab	P value	Pre-emicizumab	Post-emicizumab	P value
Median ABR (IQR)	4 (3–7.8)	0 (0)	0.003	3 (2–14)	0 (0)	0.027	4 (4–7)	0 (0–0.5)	0.042
Zero bleeding events in 6 months, no. (%)	1 (8.3)	11 (91.7)	0.002	1 (14.3)	7 (100)	0.031	0 (0)	4 (80)	0.125

ABR: annualised bleeding rate; IQR: interquartile range

Table 3. Bleeding data for infants/toddlers less than 2 years old.

Case	Age at emicizumab first dose	FVIII ED prior to emicizumab	Inhibitor status	FVIII ED prior inhibitor onset	Rationale for emicizumab	Maintenance regime	Duration of follow up after emicizumab	Bleeding events since emicizumab	Adverse events since emicizumab
1	4 weeks	12	No	NA	SDH and SAH during neonatal period	2-weekly	14 months	Nil	Nil
2	8 months	39	Yes	24	High-responding inhibitor titres	2-weekly	35 months	ABR 1	Nil
3	12 months	58	No	NA	SDH and IPH bleed at 10 months	2-weekly	21 months	Nil	Nil
4	21 months	24	Yes	24	High-responding inhibitor titres	4-weekly	4 months	Nil	Nil

ABR: annualised bleeding rate; FVIII ED: factor VIII exposure day; IPH: intraparenchymal haemorrhage; NA: not applicable; SAH: subarachnoid haemorrhage; SDH: subdural haemorrhage

Table 4. Summary of surgical procedures.

Surgical procedure	Inhibitor status	Inhibitor level prior operation	Preoperative FVIII	Postoperative FVIII	Preoperative bypass agent	Postoperative bypass agent	Postoperative bleeding
Port removal	Yes	360 BU	Nil	Nil	2 mg (0.09 mg/kg) rFVIIa given at induction	2 mg (0.09 mg/kg) rFVIIa given once postoperative	Nil
Port removal	Yes	Not detected	750 U (80 U/kg) given once at induction	750 U (80 U/kg) given every 8 hours and gradually reduced	Nil	Nil	Nil
Port removal	No	NA	3500 U (50 U/kg) given once at induction	3500 U (50 U/kg) given every 8 hours and gradually reduced	Nil	Nil	Nil
Circumcision	Yes	9.5 BU	Nil	Nil	3 mg (0.09 mg/kg) rFVIIa given at induction	3 mg (0.09 mg/kg) rFVIIa given once postoperative	Nil
Burr hole drainage	Yes	Not detected	750 U (80 U/kg) given once at induction	750 U (80 U/kg) given every 8 hours and gradually reduced	Nil	Nil	Nil
Wisdom tooth extraction	No	NA	2000 U (60 U/kg) prior procedure	2000 U (60 U/kg) Daily x 3 days	Nil	Nil	Nil

NA: not applicable; FVIII: factor VIII; rFVIIa: recombinant activated factor VII

Table 5. Summary of patients on emicizumab and immune tolerance induction (ITI).

Patient	Age of initiating emicizumab (years)	Prior initiation of emicizumab		ITI regime while on emicizumab	ITI duration while on emicizumab (months)	Total duration on ITI (months)	Current status	Last inhibitor titre (BU) as of July 2022
		Peak inhibitor titre (BU)	Last inhibitor titre (BU)					
1	0.7	5.5	5.5	50 U/kg FVIII 3x/week	2	3	Maintenance ITI with 30 U/kg FVIII 1x/week	0.25
2	1.75	11	8.5	Nil	4	4	Active ITI	26
3	2.25	8	8	30 U/kg FVIII 2x/week	19	9	Maintenance ITI with 30 U/kg FVIII 1x/week	0.4
4	2.5	10	10	Nil	13	13	Active ITI	32.5
5	5.75	3300	1200	100 U/kg FVIII daily	17	33	Stopped ITI after 33 months	345
6	13	24	24	50 U/kg FVIII 3x/week	25	25	Active ITI	3.5
7	49	26	11.5	Nil	6	6	Maintenance ITI with 50 U/kg EOD	Negative

EOD: every other day; FVIII: factor VIII; ITI: immune tolerance induction

patients with no inhibitors aged less than 12 years (10 were under the age of 2 years) with a very low ABR achieved on emicizumab and an excellent safety profile.¹⁹ Mason et al. described 4 cases of previously untreated aged less than 2 years in whom emicizumab was safe and effective in preventing bleeds.²⁰ Our study adds to the current pool of real-world data, demonstrating the effectiveness and safety of emicizumab use for prophylaxis in children with and without inhibitors, under 12 years of age and within our subpopulation of children under 2 years of age.

Similar to the case series of 4 patients by Mason et al. and the case report by Bush et al., our study shows that early initiation of emicizumab prophylaxis in infants with severe haemophilia A and intracranial haemorrhage in the absence of inhibitors is effective in preventing subsequent bleeds.^{20,21} The subcutaneous mode of administration for emicizumab makes it appealing for use in younger children, including infants, as it allows the initiation of prophylaxis at an earlier age when venepuncture can be very challenging in the absence of a central venous access device.

Early initiation of emicizumab prophylaxis before 50 EDs to FVIII puts these patients at a prolonged risk of FVIII inhibitor development that may subsequently occur when patients are re-exposed to FVIII after a bleed. One option will be to expose the patient to FVIII up to approximately 50 EDs. Our centres had initiated emicizumab in only 1 patient without inhibitors before 50 EDs. We opted to continue FVIII exposure until 25 EDs before discontinuing regular FVIII administration and had documented no FVIII inhibitor development during the study follow-up period. Several upcoming clinical trials on emicizumab use in previously untreated patients (PUPs), i.e. the HAVEN 7 (NCT04431726); the Emicizumab PUPs and Nuwiq ITI Study (NCT04030052); and The Hemophilia Inhibitor Prevention Trial (NCT04303559), will help provide further guidance in this aspect.

Our centres adopt a more conservative approach in periprocedural management for haemophilia A patients on emicizumab undergoing surgical procedures. Our study reported more minor surgical procedures being given preoperative and postoperative factor replacement (either FVIII or rFVIIa) compared with other studies. Previous real-world studies on emicizumab reported no or a single additional factor replacement given for minor procedures.^{19,22,23} There is a wide variation in practice regarding periprocedural factor replacement. The reported surgical experience from the HAVEN 1–4 studies has also concluded that emicizumab alone provides adequate

coverage for patients undergoing minor procedures, with over 90% having no postoperative bleeds without additional factor administration.²² However, increasing real-world data have shown that centres are still using periprocedural replacement strategies. Multiple observational studies have reported that the majority of patients undergoing minor procedures like port removal still receive pre-operative doses of factor replacement.^{18,19} Although reducing the amount of periprocedural factor administration would decrease cost, there are no clear guidelines for optimal periprocedural dosing in children with haemophilia on emicizumab prophylaxis. Our centres have chosen a conservative approach to minimise surgical bleeding, even in minor procedures.

The concomitant use of ITI and emicizumab in patients with inhibitors were not studied in the initial HAVEN studies. The AKATSUKI study will prospectively evaluate the use of emicizumab during and after ITI, and we await the emerging data.²⁴ For now, we have limited real-world data to understand the efficacy and safety of combined therapy. While emicizumab offers good bleeding prophylaxis, ITI remains as an important option for inhibitor eradication and restoration of haemostatic response to allogenic factor VIII, especially in the paediatric population with a higher risk of traumatic bleeds. Our findings mirror other small case series on the safe use of ITI and emicizumab without thrombotic complications.²⁵ In addition, there are emerging data to suggest that emicizumab may enhance ITI responses.²⁶ The optimal dosing of ITI is also not clear. For our patients, we used a lower dose ITI regime, taking into account patient preferences for less frequent infusions and cost considerations. This is lower than the ITI doses published so far with the Atlanta protocol using dosages of 50–100 IU/kg 3 times per week.²⁵

Limitations of this study include the short study period, small sample size, and retrospective data collection from the adult centre. Due to the retrospective nature of data collection for the 3 adult patients, bleeding events that were not documented in the medical record may not have been included. However, this likely would be similar before and after emicizumab, and hence would have been accounted for when comparing each patient's ABR pre- and post-emicizumab.

CONCLUSION

In conclusion, this study shows that emicizumab effectively protects against bleeding for haemophilia A patients with and without inhibitors,

including in children less than 12 years old, with a reduction in ABR and minimal periprocedural bleeding symptoms following periprocedural factor replacement. However, many questions on the use of emicizumab remain. These questions include whether early initiation of emicizumab will mask or delay inhibitor development, whether there is a role of concomitant FVIII replacement to prevent inhibitor development, and whether there is a role for ITI in patients with inhibitors on emicizumab. There is also a need for guidelines on the optimal dosing for periprocedural factor replacement in haemophilia A patients on emicizumab. Large, prospective studies will be necessary to answer these questions and provide more guidance in using this novel therapy.

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