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Emicizumab Prophylaxis in Hemophilia A

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ABSTRACT

Emicizumab is a monoclonal antibody that bridges activated factor IX (FIX) and factor X (FX) to replace the function of missing activated factor VIII (FVIII) in hemophilia A patients irrespective of FVIII inhibitor status. This study assessed the effectiveness of emicizumab in preventing bleeding episodes in children with hemophilia A. This prospective observational study included patients with moderate to severe hemophilia A who were undergoing episodic FVIII replacement therapy. The primary endpoint was the difference in annualized bleeding rates (ABR) and the secondary endpoint was the difference in Hemophilia Joint Health Score (HJHS) before and after emicizumab prophylaxis. A total of 17 male hemophilia patients were included, the mean age was 7.5 (SD: ±2.3) years, and most of them had moderate hemophilia A [63.3%]. Before prophylaxis, the median ABR was 18 (interquartile range [IQR]: 12–28), and 93.3% of patients had ABR greater than eight, whereas after prophylaxis the median ABR decreased significantly (median [IQR]: 0 [0.0–0.4], $p < 0.001$), and 56.7% had zero bleeds. ABR was not significantly different in patient with and without FVIII inhibitors. The HJHS scores significantly improved after prophylaxis (10 vs. 2.5, $p < 0.001$). The bleeding events were reduced significantly (17 vs. 0.0, $p < 0.001$), and zero new target joints were reported after prophylaxis. Most of the patients [93.3%] did not face any serious adverse events after prophylaxis. Emicizumab prophylaxis was associated with a significantly lower rate of bleeding events among participants with hemophilia A, regardless of inhibitor status.

Keywords: *Annualized Bleeding Rate, Efficacy, Emicizumab, Hemophilia A, Prophylaxis, Safety*

INTRODUCTION

Hemophilia is one of the inherited bleeding disorders with a distinct genetic, epidemiological, biochemical, and clinical profile[1]. Hemophilia is caused by a mutation in the factor VIII (FVIII) gene that causes a deficiency or dysfunction of coagulation clotting factor. A severe clinical bleeding phenotype, evident as spontaneous bleeding, becomes apparent when the FVIII level drops below 1% of the normal range in most hemophilia A patients.[2] Among the prominent indicators of hemophilia A is intra-articular bleeding, especially in the knee, elbow, and ankle joints. The recurrence of bleeding within joints is the chief contributor to morbidity, gradual and irreversible joint impairment, and the occurrence of hemophilic arthropathy in patients with hemophilia A.[3]Replacement of the missing FVIII with FVIII infusion is used to treat bleeding, which can occur in the muscles, skin, and mucous membranes, as well as joints. Replacement therapy in hemophilia A is related with favorable outcomes, including enhancement of quality of life[4], reduced musculoskeletal complications,[4,5] and lower morbidity and mortality[4,6]. However, administering episodic FVIII replacements does not change the inherent course of spontaneous bleeding, eventually leading to musculoskeletal damage and other complications due to bleeding. Therefore, the widely accepted practice of using prophylaxis, in which a clotting factor is administered to prevent spontaneous bleeding and sustain protective FVIII plasma trough level, is being adopted for hemophilia patients[7]. The primary concerns in hemophilia A replacement therapy are the development of anti-FVIII neutralizing antibodies (inhibitors) and the increased treatment workload due to intravenous administration and prevention efforts.[8,9] Inhibitors arise as the most challenging complication of replacement therapy, affecting as many as 30% of hemophilia A patients and undermining the effectiveness of replacement therapy.[10,11] Thus, non-factor replacement treatments for hemophilia A have been developed due to the high treatment burden and lower therapeutic efficacy of FVIII concentrate in hemophilia patients with inhibitors. The monoclonal

antibody and FVIII mimetic antibody, emicizumab, is one of the few registered non-replacement therapies used worldwide to treat hemophilia A. Emicizumab is a recombinant, humanized, monoclonal bispecific modified immunoglobulin G4 (IgG4) antibody that bridges activated factor IX and factor X to restore the function of missing activated FVIII in hemophilia A.[12] Due to its half-life lasting around 30 days, emicizumab necessitates less frequent administration via the subcutaneous route. Moreover, routine prophylactic dosing with this agent eliminates the need for regular laboratory monitoring, rendering it a compelling option for prophylactic treatment in individuals with hemophilia A. Because emicizumab lacks any structural homology with FVIII, it is not anticipated to trigger the development of FVIII inhibitors and can function irrespective of the presence of FVIII inhibitors.[13]Emicizumab has demonstrated efficacy in bleeding prevention, reducing annualized bleeding rates (ABRs[14,15,16,17]and long term administration of emicizumab are well–tolerated with no thromboembolic episodes and no neutralizing anti-emicizumab antibody appearing during the course of treatment in patients with hemophilia A.[17,18]Because of improved pharmacokinetic profile and subcutaneous administration, emicizumab is likely to have a direct impact in reducing treatment and disease burden in hemophilia A patients.

MATERIALS AND METHODS

Study design and participants

This single-center, observational study was conducted in the Bangladesh Shishu Hospital & Institute hemophilia treatment center (HTC) for a period of 4 years, from January 2021 to December 2024. The study protocol was approved by ethical review committee of Bangladesh Shishu Hospital & Institute. A total of 17 hemophilia A patients were fulfilled the selection criteria were selected. The selection criteria involved patients with severe hemophilia A and moderate hemophilia A with severe bleeding phenotype with ABR of > 8 irrespective of FVIII inhibitor status. Hemophilia individuals with intracranial hemorrhage who were receiving episodic FVIII replacement therapy, were eligible to participate. Participants who had suitable hematological, hepatic, and renal functions were included. Suitable hematologic function was defined as having a platelet count ≥100,000/μL and a hemoglobin level of ≥10 g/dL. Suitable hepatic function was defined as having a total bilirubin level ≤1.5 times the upper limit of normal (ULN) and both AST (aspartate aminotransferase) and ALT (alanine aminotransferase) levels of less than or equal to three times the upper limit of normal at the time of screening. Suitable renal function was defined as having a serum creatinine level ≤2.5 times the upper limit of normal and a creatinine clearance of ≥30 mL/min, defined by Cockcroft–Gault formula. All participants and their legal guardians were informed details about emicizumab, study characteristics, and purpose of the study in an easily understandable way. All information regarding the benefits and hazards of the study was delivered to all the participants and their legal guardians, and only those who agreed to participate after written informed consent were included in the study. The research was conducted following the guidelines outlined in the Declaration of Helsinki and adhering to Good Clinical Practice. Information was gathered via an interview utilizing a structured questionnaire.

Study procedure

Before administration of emicizumab prophylaxis therapy, all patients were screened for FVIII inhibitors. Among the 17 patients, eight hemophilia A patients had FVIII inhibitors and 9 had no FVIII inhibitors. The ABR was calculated from the previous 12 months of bleeding history using the formula of the number of reported bleeding events, divided by the number of months in the reporting time window, and multiplied by 12. The joint health was evaluated by HJHS, which incorporates nine parameters: swelling (0–3), duration of swelling (0–1), muscle atrophy (0–2), crepitus on motion (0–2), flexion loss (0–3), extension loss (0–3), joint pain (0–2), strength (0–4) for elbows, knees, and ankles, and a global gait score (0–4). The HJHS scores range from 0 to 20 per joint and the global gait score ranges from 0 to 4, resulting in a total HJHS score from 0 to 124 points. A higher score indicated a worse joint health (20). Emicizumab prophylaxis was administered by subcutaneous injection. Prophylactic treatment plan consisted of four initial loading doses of 3 mg/kg bodyweight per week, followed by a maintenance dose of 3 mg/kg every 2 weeks for 4 years. Individuals who had previously undergone episodic FVIII replacement therapy before joining the study were allowed to continue their usual prophylactic routine until after the second emicizumab loading dose, to prevent bleeding incidents prior to achieving sufficient emicizumab levels. Throughout the study period, patients and their caregivers were properly instructed to keep records of every breakthrough bleeding event and inform the HTC. Patients were followed up regularly and at each visit, detailed history of breakthrough bleeding was recorded regarding site, and severity of bleed, whether spontaneous or traumatic, and what management was taken for bleeding control. Significant bleeding events were managed with FVIII replacement therapy at HTC. For patients with inhibitor, breakthrough bleeding was managed with fresh frozen plasma (FFP) and tranexamic acid, a synthetic derivative of lysine used as an antifibrinolytic to treat major bleeding. Any side effect of the drug was properly evaluated. At each visit, bodyweight was taken for dose adjustment.

Statistical analysis

We used descriptive statistics to demonstrate the information of the participants who were enrolled. Continuous data were expressed as means and standard deviation (SD) or median and interquartile range (IQR) depending on the distribution of data. Categorical variables were expressed as frequencies and percentages. Comparisons of ABRs, number of bleeding

events, and HJHS before and after prophylaxis were assessed by Mann–Whitney U test and Wilcoxon signed rank test, where p-value less than 0.05 was considered significant.

RESULTS

Demographic and bleeding characteristics

All 17 male hemophilia A patients received a subcutaneous loading dose of emicizumab at 3 mg/kg once weekly for the initial 4 weeks, and then 3 mg/kg once every 2 weeks as maintenance regimen. Among the hemophilia A patients, the mean age of the patients was 7.5 (SD: ±2.3) years, which ranged from 1 to 18 years and the median age of first bleeding event was 7.5 (IQR: 6.0–13.5) months. Most of the patient had moderate hemophilia A [63.3%]. At baseline, the presence of FVIII inhibitor and target joint was 47% and 86.7%, respectively, and all the patients took episodic FVIII replacement therapy. The median bleeding event was 23 (IQR: 16–32), and life-threatening bleeding like intra-cranial bleeding was reported in 29.41% (Table 1).

Table 1: Baseline demographics and disease characteristics of hemophilia A patients (n = 17).

Variable	n	%
Age (years)		
Up to 12 years	7	41.18
12–18 years	10	58.82
Mean ± SD	7.7 ± 3.22	
Travel time from residence to HTC, BSH&I (h)		
<2 hours	3	17.65
2–5 hours	6	35.30
>5 hours	8	47.06
Age at first bleeding (months)		
<6 months	6	35.29
6-12 months	10	58.82
>12 months	1	5.88
Hemophilia A severity at baseline		
Moderate	8	47.06
Severe	9	52.94
Presence of target joint		
Yes	6	35.30
No	11	64.70
Prior treatment		
Episodic factor replacement	17	100
Regular prophylaxis	0	0
Bleeding event in the 12 months before study entry		
Median [IQR]	20 [15–30]	
Life-threatening bleeding event (n = 6)		
Intracranial	5	83.33
Intra-abdominal	1	16.67
Inhibitor status among study population (n 17)		
Inhibitor present	12	70.59
Inhibitor absent	5	29.41

Abbreviations: FVIII, coagulation factor VIII; HTC, hemophilia treatment center; IQR, interquartile range.
[a] Target joints were defined as major joints (e.g., hip, elbow, wrist, shoulder, knee, and ankle) in which at least three bleeding events occurred over a period of 24 weeks.

Table 2: Comparison of HJHS, ABR with inhibitor status, and bleeding events before and after emicizumab prophylaxis (n = 17).

	Before prophylaxis n (%)	After prophylaxis n (%)	p-Value *
HJHS			
Median [IQR]	9.0 [7.5–15.5]	2.0 [0.0–3.2]	<0.001
0	1 (5.88)	12 (70.59)	
1–10	8 (47.06)	4 (23.53)	
11–20	6 (35.30)	1 (5.88)	

>20	2 (11.77)	0(0)	
ABR with inhibitor, median [IQR]	28.0 [23.0–60.0]	2.0 [0.0–11.5]	<0.001
ABR without inhibitor, median [IQR]	30.0 [25.0–60.0]	1.0 [0.0–4.0]	<0.001
Bleeding events, median [IQR]	18 [14–26]	0.0 [0.0–2.0]	<0.001

Abbreviations: ABR, annualized bleeding rate; HJHS, Hemophilia Joint Health Score; IQR, interquartile range. * p-Value obtained by Wilcoxon signed rank test.

When assessing the HJHS before administration of emicizumab, the median HJHS score was 9.0 [7.5–15.5], and about half of the patients [47.06%] had an HJHS from 1 to 10, while 6 [35.29%] patients had HJHS from 11 to 20. After prophylaxis, the score was reduced to 2. [0.0–8.2], and 12 [70.59%] patients had an HJHS of 0 while, 4 [23.53%] patients had a HJHS 1. Wilcoxon signed rank test showed that the HJHS of the patients significantly reduced after prophylaxis ($p < 0.001$) (Table 2).

After emicizumab prophylaxis, the bleeding events were significantly (88.23%) reduced ($p < 0.001$). Among the 2 patients who had new bleeding event during emicizumab regimen, 11.76% had only joint bleeding (Table 2) and zero new target joint bleeding was observed. The ABR decreased significantly in both patients with and without inhibitors ($p < 0.001$).

Table 3: Summary of adverse events in patients receiving emicizumab (n = 17).

Adverse events	n	%
No adverse events	15	88.23
Allergic reaction	1	5.88
Sleep disturbance	1	5.88

DISCUSSION

The results from the present study suggested that emicizumab could offer satisfactory protection against bleeds and clinically significant bleeding control irrespective of FVIII inhibitor status, consistent with previous study findings.[14,15,19] The ABR and HJHS of the patients were significantly reduced after prophylaxis in comparison to prior no prophylaxis. After prophylaxis, majority [88.23%] of patients had a 100.0% reduction of ABR. There was no significant difference between patients with or without inhibitor regarding ABR. Most of the patients did not face any adverse events. Additionally, despite majority of the participants presented with target joints at baseline, 100% of patients reported zero treated target joint bleeds after receiving emicizumab prophylaxis, which was higher than the published studies of both standard and extended half-life FVIII prophylaxis regimens[3,20,21] indicating that emicizumab prophylaxis given subcutaneously can provide effective bleed prevention. This is the first study to investigate the efficacy and safety of emicizumab prophylaxis in children with hemophilia A, both with and without FVIII inhibitors in Bangladesh, a lower middle-income country where only 5.5% of hemophilia A patients receive prophylactic treatment and most of the patients cannot afford standard treatment and are receiving inadequate on-demand therapy for hemophilia A.[22] Majority of the participants included in the study were between 12 to 18 years, had spontaneous bleeding episodes of more than 20, were mostly moderate cases of hemophilia A, and did not have FVIII inhibitors or a record of ITI therapy or prior use of bypassing agents, which was anticipated and consistent with demographic information on the hemophilia A population in previous studies.[15,23] A total of 88.23% of the participants who received emicizumab prophylaxis had zero bleeding events during the study along with an ABR of 0.0 (IQR: 0–0.4). These positive outcomes confirm previously reported results of a phase-1 clinical trial[15], and are consistent with a series of HAVEN studies carried out among children, adults, and adolescents with hemophilia A. In the HAVEN 1 study, weekly emicizumab was well tolerated and linked to low rate of ABR in adults and adolescents (ABR: 2.9) with hemophilia A and FVIII inhibitors, and a significant number of participants experienced zero treated bleeds [63%]. Similarly, in HAVEN 2, pediatric patients with hemophilia A and FVIII inhibitors who received weekly emicizumab achieved an even lower ABR [0.3], with a large proportion reporting zero treated bleeds [77%].[15,19] The reduction in the ABR and the higher percentage of participants experiencing zero bleeds are likely linked to a lower occurrence of joint damage and a decreased frequency of target joints in the pediatric population. In our study the reduction in ABR and HJHS score was not significantly different in children and adolescents after taking emicizumab, which may be attributable to the fact that the sample size in this study was small to demonstrate the differences. Additionally, in our study after 4 years of emicizumab prophylaxis, the percentage reduction in ABR was 88.23%–100%, which was similar to reductions reported in other studies.[24,25] The substantial decrease in bleeding incidents among patients using emicizumab prophylaxis, as opposed to those without any prophylactic treatment, can be attributed to a notable enhancement in the quality of life and overall health status of patients diagnosed with hemophilia A.[26] We found no evidence that the efficacy of emicizumab was affected by FVIII inhibitor status ($p = 0.166$), although this conclusion should be made cautiously because of the small number of patients with inhibitors in this study. Emicizumab prophylaxis led to clinically relevant improvement in joint health. The median HJHS decreased from 9.0 [7.5–15.5] to 2.0 [0.0–8.2). No patient had deterioration in joint health score and zero target joint was observed after 4 years of emicizumab, indicating persistent joint health benefits with emicizumab prophylaxis. Similarly, the HAVEN 3 clinical trial

reported a significant improvement in joint health scores in adolescents and young adults and in those with target joints after 48 weeks of emicizumab.[12] Safety investigations showed that most of the patients [88.23%] did not face any adverse events after prophylaxis, whereas one [5.88%] patient had a mild allergic reaction at injection site and another patient had sleep disturbance. All the events were mild and had spontaneous resolution. No serious adverse events and thromboembolic events or thrombotic microangiopathies were reported, which was similar to findings to previous studies.[16,18]

CONCLUSION

The study results suggested that emicizumab prophylaxis administered subcutaneously, led to a significant reduction in the bleeding rate compared with no prophylaxis among hemophilia A patients, regardless of the presence of FVIII inhibitors.

Conflict of Interest: *None*
Source of Fund: *Nil*

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