RESEARCH ARTICLE
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Evaluation of Safety and Efficacy of Emicizumab Prophylaxis in Egyptian Pediatric Patients with Hemophilia A: Single Center Cross Sectional Study

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Abstract
Purpose: Hemophilia A (HA) is an X-linked hereditary bleeding disorder caused by deficiency of coagulation factor VIII activity. Emicizumab is a bispecific monoclonal antibody that replaces the function of activated FVIII and prevents bleeds in patients with hemophilia A. Emicizumab is expected to reduce the risk of severe bleeds in those patients with their subsequent complications. However, data about its safety and efficacy in patients with hemophilia A is limited. We aimed to evaluate safety and efficacy of Emicizumab prophylaxis in Egyptian pediatric patients with HA.
Methods: A prospective cohort study was conducted on 88 HA patient who received prophylaxis with Emicizumab. Breakthrough bleeding episodes as well as annualized bleeding rate(ABR) were reported for all patients before and after Emicizumab prophylaxis. All adverse events during prophylaxis were reported to evaluate the safety of Emicizumab.
Results: Joint bleeds were present in 94 % of the patients. 58% of them had one target joint, 36.4% had more than one target joint while 5.6% had no target joints. 17% of patients were positive for FVIII inhibitors. The median annualized joint bleeding rate (AJBR) was reduced remarkably after Emicizumab prophylaxis (36 before versus zero after Emicizumab. Also, the median ABR was 48 before Emicizumab versus zero after Emicizumab. Eight patients developed mild breakthrough bleeding episodes. The most common adverse events were local reaction at the injection sites, headache, arthralgia, fever and diarrhea.
Conclusion: Emicizumab prophylaxis was associated with significantly lower rate of bleeding events in patients with HA with and without inhibitors. The majority of patients had zero bleeds with Emicizumab prophylaxis.
Keywords: Emicizumab, Safety, Efficacy, hemophilia A

Introduction

Hemophilia A is an X-linked, recessive disorder caused by deficiency of functional plasma clotting factor VIII (FVIII), which may be inherited or arise from spontaneous mutation. patients with hemophilia A usually manifest with prolonged and excessive bleeding either spontaneously or after trauma [1]. Patients with severe hemophilia A may have serious joint bleeding, soft tissue bleeding, muscle bleeding and life-threatening bleeding manifestations such as intracranial hemorrhage [2]. Factor VIII inhibitors, develop in 25 to 30% of patients with severe hemophilia A and render FVIII replacement therapies ineffective, thus exposing hemophilia Patients to a greater risk of spontaneous and traumatic bleeding episodes. Those patients who develop FVIII inhibitors have limited treatment options for example: bypassing agents (BPAs), including activated prothrombin complex concentrate and recombinant activated FVII which offer alternative treatment options but are associated with a greater burden of treatment and inconsistent bleeding control [3].

Replacement therapy is the main treatment for hemophilia A either in case of bleeding episodes only (on demand), or with regular infusions of FVIII concentrates to avoid bleeding episodes (prophylaxis) [4]. Regular prophylactic intravenous infusion of factor VIII is the current treatment for patients with severe hemophilia A [5]. However, because of the half-life of factorVIII, a minimum of two infusions per week are necessary for maintaining protective trough levels, which results in a substantial treatment burden and an unsatisfactory level of care for persons who are unable to adhere to this strategy [6]. Despite regular prophylaxis, clinical and subclinical bleeding events may occur. Thus, treatments with a high efficacy and reduced burden are still needed [7].

Emicizumab is a humanized bispecific IgG4 monoclonal antibody administered subcutaneously that bridges activated factor IX and factor X to replace the function of missing activated factor VIII, thereby restoring hemostasis [8]. Emicizumab is approved for bleeding prevention in people with hemophilia A with and without inhibitors. The reduced dosing frequency, subcutaneous route of administration, and significantly reduced annualized bleeding rates allowed a variety of individuals with hemophilia A to switch to Emicizumab to prevent bleeds [9].

Despite the fact that Emicizumab safety profile was largely favorable, the danger of thrombotic microangiopathy (TMA) remains a major cause for concern. TMA events happened only when high dosages of APCC have been given either with rFVIIa or alone [9]. We conducted this research to evaluate safety and efficacy of Emicizumab prophylaxis in Egyptian Patients with Hemophilia A.

Study populations

This cohort study was carried on 88 children diagnosed with congenital hemophilia A who were followed up at pediatric hematology unit and outpatient clinic of Zagazig University hospitals, during the period from December 2020 to December 2021.

Treatment protocol before Emicizumab:

All patients were previously treated with on demand standard factor VIII replacement therapy before starting Emicizumab. The dose of factor VIII was calculated in Units/kg according to site of bleeding). None of our patients received standard factor VIII replacement therapy as a prophylaxis. The study period of pre-switch to Emicizumab was one year.

Treatment protocol of Emicizumab prophylaxis:

All patients were receiving Emicizumab as a prophylactic therapy. Emicizumab administered subcutaneously in a dose of 3 mg/kg every week for 4 weeks (loading dose) followed by 3 mg/kg every 2 weeks (maintenance dose) for the remainder of the 1-year treatment period [10]. Emicizumab was given at the out-patient hematology clinic under close medical supervision. Emicizumab in our study was covered by health insurance and approved for patient older than one year and provided under regular clinical practices.

Patients were considered eligible for the study if they met the following inclusion criteria:

- Approval to sign an informed written consent.
- Patients with severe hemophilia A
- Patients with moderate hemophilia A with severe bleeding profile and/or target joints
- Age > 1year and < 18 years

Methods

All patients were subjected to:

- Complete history taking with special emphasis on detailed bleeding history
- Complete physical examination including vital signs, site of bleeding, examination of affected joint.
- Recording of Annualized bleeding rate before and after receiving Emicizumab therapy.
- Recording of breakthrough bleeding episodes (numbers, severity, treatment given and duration)

All patients were followed up for at least six months, and adverse events were reported in accordance with the standardized Medical Dictionary for Regulatory Activities by System Organ Class and selected term The WHO toxicity grading scale was used to define toxicity grade [11].

Classification of severity of hemophilia [12]**:**

The severity of hemophilia A was classified according plasma levels of factor VIII activity:

- Plasma levels of factor VIII activity<1% indicates severe Hemophilia A.
- Plasma levels of factor VIII activity>1% and <5% indicates moderate Hemophilia A.
- Plasma levels of factor VIII activity>5% and <40% indicates mild Hemophilia A.

Definitions

Target joint: defined as 3 or more spontaneous bleeds into a single joint within a consecutive 6-month period [12].

Muscle bleed: an episode of bleeding into a muscle, determined clinically and/or by imaging studies, generally associated with pain and/or swelling and limitation of movement [12].

Ethical approval

This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1964, as revised in 2000. The study protocol Number (8063) was approved by the Research Ethics Committee of the Faculty of Medicine, Zagazig University. Informed written consent and/or assent were obtained from the parents or guardians of each child.

Statistical analysis

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 26 (IBM, Armonk, NY, USA). Categorical variables were described using their absolute frequencies. Shapiro-Wilk test was used to verify assumptions for use in parametric tests. Quantitative variables were described using median and interquartile range. To compare quantitative data between two groups, Mann Whitney test (for not normally distributed data) was used. To assess strength and direction of correlation between two continuous variables, Spearman rank correlation coefficients (for not normally distributed data) was used. To compare the same variables between two points of time within same group, paired sample t test (for normally distributed data) and Wilcoxon signed rank test (for not normally distributed data) were sued. The level statistical significance was set at $P<0.05$.

Results

In the current prospective cohort study, 88 children diagnosed with hemophilia A were enrolled. Their age ranged from 2 to 15 years with a median of 6 years. The median age at diagnosis was 3 months. Regarding initial clinical presentation, skin and subcutaneous bleeding was present in all patients. Joint bleeding was found in 94% of patients, mucosal bleeding in 54.8% of patients and muscle hematoma in 11.4% of the patients. 92.2% of the studied patients had severe hemophilia A. 17% of patients were positive for FVIII inhibitors [Table 1].

Joint bleeding was present in 94% of the patients. 58% of patients had one target joint, 36.4% had more than one target joint while 5.6% had no target joint. Knee joint, elbow joint and ankle joint were the comments affected joints (68%,26% and 25% respectively) [Table 2].

The median annualized bleeding rate was 48 before treatment with Emicizumab versus zero after the use of Emicizumab ($p<0.001$). Percent reduction in annualized bleeding rate ranged from 95.8% to 100% with median 100% [Figure1]. The median annualized joint bleeding rate was 36 before treatment with Emicizumab versus zero after the use of Emicizumab ($p<0.001$) with median percent reduction of 100%.

Only 8 patients suffered mild breakthrough bleeding episodes (5 patients had hemarthrosis, 2 patients had head hematoma and 1 patient had epistaxis). All breakthrough bleeding episodes occurred after trauma. They were mild and improved with infusion of a single dose of FVIII [Table 3]. As regards head hematoma, it was external and not associated with any intracranial or subdural bleeding. Both head hematomas occurred in young children (age of patients was 3 and 4 years). All breakthrough bleeding episodes occurred in the maintenance phase of Emicizumab (1 to 3 days before the scheduled dose).

The most common adverse events were local reaction at the injection sites (19 patients, 21.6%), headache (12 patients, 13.6%), arthralgia (11 patients, 12.5%), fever (4 patients, 4.5%) and diarrhea (3 patients, 3.4%). All adverse events were mild and resolved without treatment [Table 3]. No thrombotic events were reported in our study cohort.

There was no significant relationship between severity of factor VIII deficiency and any of percent reduction of annualized bleeding rate or incidence of breakthrough bleeding after Emicizumab prophylaxis($p>0.05$). Moreover, no significant relationship was found between factor VIII inhibitor status and any of percent reduction of annualized bleeding rate or incidence of breakthrough bleeding after Emicizumab prophylaxis($p>0.05$).

Discussion

In the current research, concerning the initial presenting symptoms, skin and subcutaneous bleeding was present in all patients. Joint bleeding was found in 94% of patients, mucosal bleeding in 54.8% of patients and muscle hematoma in 11.4% of patients. In agreement with our data, Levy et al found that 163/193 (84%) of the patients had bleeding episodes that happened mainly in their joints or muscles. Also, Callaghan et al, reported that most of bleeding episodes were in the joints and 61.0% of the studied hemophilia patients had target joints [13,14]. Additionally, Mccary et al, found that 47.4% of patients had mucosal bleeding, 36.8% of patients had soft tissue/muscle bleeding [15].

In our study, 93.2% of the patients had severe hemophilia A while 6.8% of patients had moderate hemophilia A. 17% of the studied patients had positive testing for factor VIII inhibitors. The incidence of inhibitors observed in our study was comparable to that in other studies where, Shah et al, reported an inhibitor rate of 20.6% of their study cohort (50 out of 243 patients) [16]. Also, Gouw et al, found that Inhibitory antibodies developed in 177 out of 574 patients (cumulative incidence, 32.4%) [17]. In a large multicenter randomized controlled clinical trial conducted by Peyvandi et al, the cumulative incidence of inhibitors was 26.8% [18]. Lower incidence of FVIII inhibitors (8.7%) were reported by Kim et al [19].

Approximately 80% of bleeding events in patients with hemophilia are intra-articular in nature, two-thirds of which are reported in the knees, elbows, and ankles [20]. In our study, Joint bleeding was present in 94% of the

patients. 58% of patients had one target joint, 36.4% had more than one target joint while 5.6% had no target joints. Knee joint, elbow joint and ankle joint were the comments affected joints (68%,26% and 25% respectively) In a large study conducted by Reding et al, a total of 113 individual target joints were reported among 59 patients. The most common sites for target joints were the ankles (47 target joints), elbows (33 target joints) and knees (27 target joints) [21]. Moreover, Abdelwahab et al reported that most of patients had 3 to 4 target joints [22].

In Egypt, the health insurance recently approves Emicizumab prophylaxis for young children with hemophilia A as a primary prophylaxis. Previously it was given only to patients with inhibitors and so experience of Emicizumab in PUPs is very limited.

In our study, the median ABR was 48 before starting Emicizumab prophylaxis. Higher ABR in our study compared to previous ones could be attributed to some factors, the most important of which is the shortage of supply of factor VIII concentrates at some times, lack of home therapy in addition to higher exposure to trauma in our locality.

Here in this study, there was successful reduction in ABR during Emicizumab prophylaxis where the median annualized bleeding rate was 48 before Emicizumab versus zero after Emicizumab prophylaxis ($p<0.001$). Percent reduction in annualized bleeding rate ranged from 95.8% to 100% with median 100%. Only 8 patients (9%) developed mild breakthrough bleeding episodes (5 patients had hemarthrosis, 2 patients had head hematoma and 1 patient developed epistaxis) which were mild and improved with infusion of single dose of FVIII.

In agreement with our results, Oldenburg et al enrolled 109 hemophilia A patients with inhibitors in HAVEN 1 study and reported that the ABR was 2.9 events (95% confidence interval [CI], 1.7 to 5.0) among participants who were randomly assigned to Emicizumab prophylaxis (group A, 35 participants) versus 23.3 events (95% CI, 12.3 to 43.9) among those assigned to no prophylaxis (group B, 18 participants), representing a significant difference of 87% in favor of Emicizumab prophylaxis ($P<0.001$) [23].

Similarly, Mahlangu et al in their comparative study on adolescents with hemophilia A without FVIII inhibitors using either maintenance dose of Emicizumab of 1.5 mg per kilogram of body weight per week (group A) or 3.0 mg per kilogram every 2 weeks (group B) or no prophylaxis (group C), found that the ABR was 1.5 events (95% confidence interval [CI], 0.9 to 2.5) in group A and 1.3 events (95% CI, 0.8 to 2.3) in group B, compared to 38.2 events (95% CI, 22.9 to 63.8) in group C; thus, the rate was 96% lower in group A and 97% lower in group B ($P<0.001$ for both comparisons). A total of 56% of the participants in group A and 60% of those in group B had no treated bleeding events, compared to those in group C, where all had treated bleeding events [24].

Pipe et al in their phase 3, multicenter, open-label, two-stage study (HAVEN 4) to evaluate efficacy and safety of Emicizumab prophylaxis found that the ABR for all treated bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds was significantly lower with Emicizumab prophylaxis compared to no prophylaxis [25].

Also, Shima et al conducted a multicenter, open-label study (HOHOEMI) in Japanese pediatric patients aged <12 years with severe hemophilia A without factor VIII (FVIII) inhibitors and divided the study participants into two cohorts either receiving maintenance doses of 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks of Emicizumab prophylaxis. The ABR for treated bleeding events were 1.3 (95% confidence interval [CI], 0.6-2.9) and 0.7 (95% CI, 0.2-2.6). All caregivers preferred Emicizumab to the patient's previous treatment [26].

Callaghan et al, in their study to evaluate the long-term outcomes with Emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies, reported that the treated ABR was 1.4 (95% confidence interval [CI], 1.1-1.7). ABRs declined and then stabilized at <1 in an analysis of 24-week treatment intervals. The mean treated ABR was 0.7 (95% CI, 0-5.0). 82.4% of participants had zero treated bleeds, 97.6% had ≤3 treated bleeds, and 94.1% reported no treated target joint bleeds. Bleeding into target joints decreased substantially with Emicizumab prophylaxis [14].

In agreement with our results, Abdelwahab et al, in their prospective cohort study on severe hemophilia A patient, reported that the bleeding rate ranged from 6-8 events/ year and it was dropped to zero bleeds after 6 months on biweekly prophylactic Emicizumab in 11(78.6%) patients. Only 3 patients experienced at least one breakthrough bleed but none into target joints [22].

Results of a single center retrospective study conducted by Hassan and Motwani on severe hemophilia A patient with and without inhibitors after receiving Emicizumab, showed that 56.8% (29/51) experienced no bleeding events, and 80.3% (41/51) had no major treated bleeds during the follow-up period. A total of 29.4% (15/51) had minor bleeds that resolved spontaneously or with antifibrinolytics. Overall, 19.6% (10/51) of the patients received additional FVIII to prevent or treat breakthrough bleeding [27].

This came in agreement with Young et al where Emicizumab prophylaxis in 85 patients diagnosed with hemophilia A and positive FVIII inhibitors was investigated in a phase 3 trial (HAVEN 2). Participants were treated with subcutaneous Emicizumab: 1.5 mg/kg weekly (group A), 3 mg/kg every 2 weeks (group B), or 6 mg/kg every 4 weeks (group C). and they found that annualized rate of treated bleeding events (ABRs) was 0.3,

0.2 and 2.2 in group A, B and C respectively with 99% percent reduction in ABR and 77% had no treated bleeding events [28]. Results of these different studies about efficacy of Emicizumab were listed and summarized in table 4.

In our study, the most common adverse events were local reaction at the injection sites (19 patients, 21.6%), headache (12 patients, 13.6%), arthralgia (11 patients, 12.5%), fever (4 patients, 4.5%) and diarrhea (3 patients, 3.4%). All adverse events were mild and resolved without treatment. No thrombotic events were reported in our study cohort. No antidrug antibodies were detected in our patients.

Pipe et al reported that the most frequent treatment-related adverse event was injection-site reaction (9 [22%] of 41 patients). No thrombotic events or development of de-novo antidrug antibodies with neutralizing potential or FVIII inhibitors [(25].

Oldenburg et al observed 198 adverse events in 103 participants receiving Emicizumab prophylaxis; the most frequent events were injection-site reactions (15% of participants). Thrombotic microangiopathy and thrombosis were reported in 2 participants each (in the primary analysis) who had received multiple infusions of activated prothrombin complex concentrate for breakthrough bleeding. No antidrug antibodies were detected [23].

Also, Young et al found in their study that the most frequent adverse events were nasopharyngitis and injection-site reactions; no thrombotic events occurred. Two of 88 participants developed antidrug antibodies (ADAs) with neutralizing potential, that is, associated with decreased Emicizumab plasma concentrations: 1 experienced loss of efficacy, and, in the other, ADAs disappeared over time without intervention or breakthrough bleeding [28].

Finally, Callaghan et al reported in their study that Emicizumab exhibited a consistently favorable long-term safety profile, with no unexpected or new safety signals. [14]. No fatalities or TMAs were reported across HAVEN 1-4, beyond those described by Oldenburg et al in the HAVEN 1 primary analysis [23]. Of 4 TEs reported, 2 were associated with concomitant aPCC use (cavernous sinus thrombosis and skin necrosis–superficial thrombophlebitis) during HAVEN 1. Of the 2 not associated with concomitant aPCC, device occlusion was reported in HAVEN 1 during weeks 25 to 48, and acute MI was reported in HAVEN 3 during weeks 145 to 168. Following the identification of TMA and TEs in association with the administration of high doses of aPCC during HAVEN 1[14].

Study limitations

One of the limitations of this study was that it included only children and adolescents with Hemophilia A. However, this was because those patients were covered by health insurance. Another limitation was that our patients were on on-demand factor VIII replacement therapy and switched to Emicizumab prophylaxis. We suggested larger multicenter study including patients on prophylaxis Factor VIII replacement therapy who will be switched to Emicizumab prophylaxis.

Conclusion

In the current study, safety and efficacy data of Emicizumab are consistent with the findings of previous studies in hemophilia A. Emicizumab was effective in terms of reduction of annual bleeding rate where the majority of patients had zero treated bleeds. Also, Emicizumab continued to demonstrate a favorable safety profile, with no discontinuations due to adverse events. Emicizumab prophylaxis seems to be an effective as well as safe treatment option for patients with hemophilia A.

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Data availability statement:

All data included in this manuscript are available upon a reasonable request from the corresponding author.

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Ethical approval: This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1964, as revised in 2000. The study protocol Number (8063) was approved by the Research Ethics Committee of the Faculty of Medicine, Zagazig University. Informed written consent and/or assent were obtained from the parents or guardians of each child.

Conflict of interest for all authors: No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Contributors' statement: All authors contributed to the study conception and design, material preparation, data collection and analysis. Tamer Hassan, Marwa Zakaria, Manr Fathy, Ahmed Farag. Eman Abdelhady and Dalia Gameil recruited patients and performed the clinical examination. Mustafa Abu Hashem participated in data collection, analysis and performing the statistics, all authors participating in writing and reviewing the manuscript. Marwa Zakaria submitted the final manuscript.

List of abbreviations:

HA: Hemophilia A, BPAs: bypassing agents ,FVIII : factor VIII, rFVIIa : recombinant activated factor VII, IgG: immunoglobulin G, TMA :Thrombotic microangiopathy, APCC : Activated Prothrombin Complex Concentrate, WHO: World Health Organization, ABR: annualized bleeding rate, ADAs :antidrug antibodies, TEs :transient ischemic attacks. MI: Myocardial infarction.

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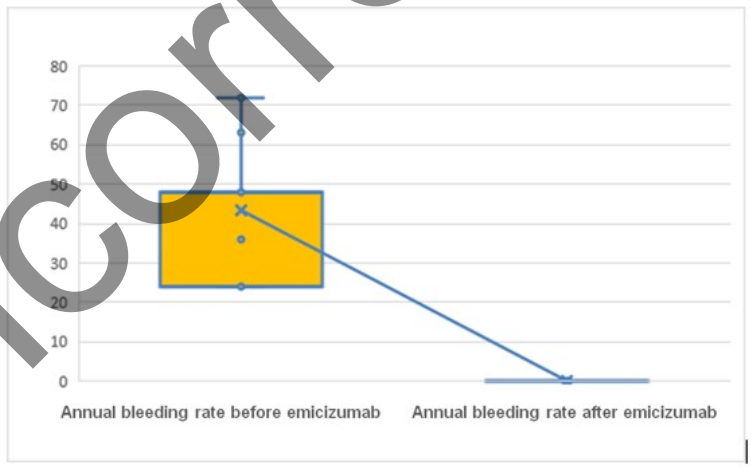

Figure 1: Boxplot showing annualized bleeding rate before and after therapy with Emicizumab.

Table 1. Demographics, clinical and laboratory characteristics of the studied patients.		
variable	Median (IQR)	Range
Age (years)	6 (4 – 10)	2 – 15
Age at diagnosis (months)	3 (1 – 6)	1 – 24
Initial clinical presentation	Patients n (88)	%
Cutaneous hemorrhage	88	100%
Joint hemorrhage	83	94.3%
Mucosal hemorrhage	57	54.8%
Muscle hemorrhage	10	11.4%
Internal hemorrhage	0	0%
Type of Hemophilia A		
Moderate Hemophilia	6	6.8%
Severe Hemophilia	82	93.2%
Inhibitor status		
Negative	73	83%
Positive	15	17%

Table 2. Frequency of the affected joints among hemophilia A patients.		
Affected joint	**Patients with hemophilia**	
	N=88	**%**
Knee		
Unilateral	53	60.2
Bilateral	7	9.8
Elbow		
Unilateral	22	25
Bilateral	1	1.1
Ankle		
Unilateral	21	23.9
Bilateral	1	1.1
Wrist		
Unilateral	2	2.27
Bilateral	0	0
Hip		
Unilateral	5	5.6
Bilateral	0	0
Target joints		
One target joint	51	58
> one target joint	32	36.4
No target joint	5	5.6

Table 3: Prevalence of breakthrough bleeding episodes and side effects in haemophilic patients receiving Emicizumab prophylaxis.		
Status during receiving Emicizumab	N=88	%
No breakthrough bleeding Breakthrough bleeding	80 8	91 9
Sites of breakthrough bleeding	N=8	%
Hemarthrosis	5	62.5
Head hematoma	2	25
Epistaxis	1	12.5
Reported Side effects during treatment with Emicizumab		
Injection site reaction	19	21.6
Headache	12	13.6
Arthralgia	11	12.5
Fever	4	4.5
Diarrhea	3	3.4

Table 4. Results of different studies about efficacy of Emicizumab in hemophilia patients.

Author	Number of Patients on demand therapy before Emicizumab	Number of Patients on prophylactic therapy before Emicizumab	Number of Patients with +ve FVIII inhibitors	Number of Patients with -ve FVIII inhibitors	Post-Emicizumab ABR (mean)	Post-Emicizumab AJBR(mean)	% of patients with Zero bleeding after Emicizumab	% reduction of ABR after Emicizumab
Oldenburg et al. 2017	109	Zero	109	Zero	2.9	NE	63%	79%
Mahlangu et al. 2018	152	Zero	Zero	152	1.3	NE	60%	68%
Pipe et al. 2019	41	Zero	41	Zero	4.5	1.7	56.1%	NE
Shima et al. 2019	Zero	12*	Zero	13	14.2	0.9	53.8%	NE
Callaghan et al. 2021	353	Zero	305	48	1.4	NE	82.4%	NE
Young, et al. 2019	22	66	85	3	0.2	NE	90%	99%

*: one patient (infant) didn't receive any factor VIII, ABR: annualized bleeding rate, AJBR: annualized joint bleeding rate, NE: not estimated