Journal for ReAttach Therapy and Developmental Diversities
eISSN: 2589-7799
2022 December; 5 (2s): 477-482

Emicizumab Prophylaxis Every Four Weeks among Hemophilia a with Inhibitors in Iraq, Multicenter Study

NidalKarim Al-Rahal[1], Oula Abdullah Najim[2] Ahmed Shemran Alwataify*[3], Israa Mustafa Almusawi[4], Ahmed Ibrahim Shukr[5], Yaser Shanyor Alsalman[6]

(1) National Centre of Hematology/ Mustansiriyah University/Iraq
(2) Pediatrician, , Basra Center for Hereditary blood Diseases/Iraq
(3) Professor of pediatrics, Babylon maternity and children hospital, Babylon hereditary blood disease center/Iraq
(4) Consultant pediatrician, Hereditary Blood Disease Center of Karbala Teaching Hospital for Children/Iraq
(5) Subspecialty in adult clinical hematology, Kirkuk Center for Oncology &Hematology/Iraq
(6) Pediatrician , Thikar Center for Hereditary blood Diseases/Iraq
dr.ahmedshemranwataify@gmail.com

Received: 14-September-2022
Revised: 15-November-2022
Accepted: 17-December-2022

Abstract

Introduction: Hemophilia A is a chronic inherited bleeding disease required recurrent intravenous infusions of FVIII or bypassing agents. Emicizumab is a novel drug used in hemophilia prophylaxis with or without inhibitors, is given subcutaneously weekly, every 2weeks or every 4 weeks.

Aim: assess safety, efficacy, quality of life and cost effectiveness of emicizumab prophylaxis treatment every 4 weeks in adult & pediatric patients with hemophilia A with inhibitor.

Methods: This is an interventional study, as open label in multi center extension in Iraqi hemophilia centers, it had been conducted from April 2021 to October 2021 on 32 hemophilia A with high titer inhibitors treated with emicizumab prophylaxis, compared with same patients in previous 6 months with episodic recombinant factor VII.

Results:- The age of patients, ranged from 1 to 46 years , 75% of patients <18years, they have statistically significant improvement in all variable factors: rate of bleeding, joint bleeding , number of hospital admission , blood transfusion , school or work absence , FISH score , EQ-5D-5L , cost effectiveness , Hb% and aPTT in 6mo of emicizumab prophylaxis therapy , in comparison to previous 6month of episodic rFVIIa treatment. Injection site reaction was the most common adverse effect, no risk of thrombosis.

Conclusion: emicizumab prophylaxis therapy every 4 weeks, is safe, effective, improve quality of life & cost effective.

Key words: - Hemophilia A with inhibitors, emicizumab, cost effectiveness, Iraq.

1. INTRODUCTION

Haemophilia is the most common and serious congenital coagulation factor deficiencies. The key to a successful long-term outcome is an efficient prophylaxis that prevent joint bleeding [1]. Prophylaxis is either regular intravenous infusion of the missing FVIII or by non-factor replacement therapy(emicizumab), which provides hemostasis through a different mechanism[2]. Patients with inhibitors with acute bleeding are treated with bypassing agents. Emicizumab is effective as prophylaxis in adults and children with or without inhibitors [3]. It's a bispecific monoclonal antibody that mimics factor VIII by binding to factors IXa and X to promote hemostasis. It is administered subcutaneously once weekly, every 2 or 4 weeks [3] .

Hemophilic patients have impairment of quality-of- life which either due to bleeding incident or permanent painful joint damage[4]. Health related quality of life can be measured by EQ-5D [5]. The Functional Independence Score for Hemophilia (FISH) has been developed to assess performance of functional activities [6].

Aims of study: -

To assess: safety, efficacy and cost effectiveness of emicizumab prophylaxis therapy in hemophilia A with inhibitor (HAI) pediatrics and adults.

2. MATERIAL & METHODS

This is an interventional study, as open label in multi center extension in Iraqi hemophilia centers: Baghdad, Basra, Hila, Karbala, Kirkuk & Thikar, it had been conducted from April 2021 to October 2021 on 32 HAI pediatrics & adults with high titer on emicizumab therapy, compared with same patients treated in previous 6 months with rFVIIa episodic therapy.

All patients and or their families legally authorized representatives were provided written informed consent for study participation.

Inclusion criteria: -

1- Congenital HAI of high titer more than 5 Bethesda unit /ml.

2- Patients were initially normal hematological, renal and hepatic functions.

3- Full history of bleeding and admission to hospital on episodic therapy with rFVIIa in the last 6 months.

Exclusion criteria:

Those with planed surgery during this time, with thromboembolic disease or high risk of thrombotic microangiopathy were excluded .

Detailed history was taken from each patient before emicizumab prophylaxis treatment regarding: bleeding attacks, joints bleeding, numbers of admission, number of rFVIIa vials consumed by patients and days of school or work absence/month for 6 months, and all parameters were assessed after 6 months of emicizumab prophylaxis therapy. Blood was aspirated from each patient for complete blood count, liver function tests, renal function tests, aPTT &hepatitis infection screen (HBsAg , HCV Ab) and HIV Ab, during rFVIIa and emicizumab therapy.

Baseline assessment for quality of life and the degree of arthropathy for each patient was performed using EuroQol 5-dimention5-level (EQ-5D-5L) [7] and (FISH) score respectively before &after emicizumab therapy.

FISH Score: depends on several factors: self- care (eating and grooming, bathing and dressing), transfers (chair and squatting) and locomotion (walking, stairs and running). Score either into Q1, Q2, Q3 and Q4 (Q1 is worst and 4 is the best). Total score: < 18 severe, 18-24: moderate and 24-32 mild [8].

Enrolled patients with HAI were treated on episodic therapy with rFVIIa in a dose of 90 microgram/kg/ IV given according the severity of bleeding usually in 3 doses in 3 hour interval in mild to moderate form, while in severe form, the dose given every 2 hour until hemostasis achieved, then shifted to 3 hour interval for 1-2 days and then increment in interval time to 4, 6, 8 and 12 hours depend on the type of bleeding[9].

In the next 6 months, the treatment was changed to emicizumab prophylaxis ,if the patient developed bleeding, he was treated on episodic therapy with rFVIIa accordingly, emicizumab was started as bolus dose of 3 mg/kg /week subcutaneously for 4 weeks , then on maintenance dose of 6 mg /kg /4wk SC for 6 months[10]. Adverse effects were assessed after each dose of emicizumab therapy including itching, skin rash, headache, pharyngitis, tonsillitis, diarrhea, nausea, vomiting, fever, deep vein thrombosis & any attack of bleeding. Cost effectiveness was calculated of both groups by US dollars, price of each vial of rFVIIa (1 mg) is 623 US dollars and each gram of emicizumab is 23 US dollars in Iraq.

Data analysis: -

Statistical analysis carried out by using SPSS version 25. Categorical variables were presented as percentages and frequencies. Continuous variables presented as mean ± SD. student t-test used to compare means between two groups. A p-value of ≤ 0.05 was considered significant.

3. RESULTS

Thirty two patients, ranged from 1 to 46 years with mean age 16.07 ± 12.32, 75% of patients were < 18 years. Demographic distribution is shown in Table (1).

There were statistically significant improvement in all variable factors in 6mo of emicizumab prophylaxis therapy, in comparison to previous 6month of episodic rFVIIa treatment, with a significant p-values, were demonstrated in Table (2).

There were a statistically significant results regarding aPTT, Hb% and platelets count before and after emicizumab therapy with a P- value 0.000, 0.005 and 0,005 respectively as shown in Table (3).

Comparing the cost effectiveness in 6 months, in US $, it was higher in rFVIIa episodic therapy (3842mg/2,316,726$) while in emicizumab prophylaxis therapy it was (54792 mg/1,260,216 $).
Regarding safety of emicizumab prophylaxis therapy, the adverse effects: Itching at site of injection was the commonest adverse effect seen in 18.75%, followed by headache and skin rash at site of injection in 9.37% each. There were no fever, nausea, vomiting, diarrhea, pharyngitis & no deep vein thrombosis.

4. DISCUSSION

The basis of haemophilia therapy is the rFVIII treatment , administered intravenously resulting in several clinical challenges as frequent injections and risk of inhibitors formation[11]. These influence negatively on patients compliance, the quality of life, emphasizing the need for better lines of therapies. One of the novel drugs used in hemophilia prophylaxis is emicizumab, which mimic FVIIIa[11].

The mean hemophilic age in this study was 16.07±12.32,while the mean body weight were 40.09± 25.77 which is located below the 3rd percentile of Center of Disease Control and Prevention (CDC) growth chart (underweight) and this is similar to that was found in Registry Report[12]). 15.62% of our patients were positive HCV Abs & 3.12% positive HBsAg. All had history of blood or blood product transfusion previously& not related to emicizumab therapy.

Our results showed superiority of emicizumab therapy over episodic rFVIIa regarding bleeding attacks and joint bleeding. There were a substantial lower bleeding rate and joint bleeding in emicizumab therapy as 1.5 ± 0.707 and 0.93± 0.34, in comparison to rFVIIa 30.5 ± 7.72 and 13.43 ± 10.02 respectively and statistically were highly significant , with P-value 0.01 & 0.000 respectively , those results are similar to Oldenberg J et al[13].
, This study showed that there was decreased bleeding rate &joint bleeding after emicizumab prophylaxis ,leading to reduction in number of hospital admission & the need for blood transfusion, with P-value 0.003& 0.018 respectively, which is compatible to Quellec SI[11].
In the current study , there were statistically significant improvement in school&work performance as there were decreased in absence days with significant P-value of 0.000 after prophylactic emicizumab therapy, this is in accordance with Rind Det al [14]. This study demonstrated improvement of joint health with higher FISH Score, increased from 21.29 ± 5.44 in episodic rFVIIa treatment to 28.88 ± 3.08 after emicizumab prophylactic therapy, with a significant p-value of 0.000.Excitingly, several studies showed that,there is a reduction in target joints after emicizumab prophylaxis, so as this study[15]. Regarding assessment of quality of life for HAI patients in this study, using (EQ-5D-5L), there was an improvement in quality of life with statistically significant P-value 0.05, this result correlates well with Oldenburg J,et al[16].This improvement in quality of life, can be explained by reduction in bleeding rate, less joint bleeding, no admission to hospital, besides SC administration of emicizumab/ 4 weeks . In the current study, there was a significant cost saving with reduction from 2,316,726 US $ in rFVIIa to 1,260,216 US $ in emicizumab therapy , without adding other medical services as nursing facilities, hospital occupancy etc. , this result was compatible to Lee H et al in Korea[17].
Regarding assessments of lab results, we noticed that aPTT was normalized with emicizumab and its level was reduced from 92.76 ± 11.15 sec during rFVIIa to 28.22 ± 5.46 sec in emicizumab and statistically was highly significant with P-value 0.000, this is similar to Bowyer A, et al[18] . Emizicumab interferes with hemostasis tests, mainly those based on aPTT. But normal aPTT in patients treated with emicizumab is not sufficient to consider normal hemostasis [19], as aPTT is normalized already at sub therapeutical emicizumab concentrations (3-5 μg / mL), whereas therapeutic levels are around 55 μg /mL [20].There were statistically significant improvement in both Hb% and platelets count during emicizumab treatment. Hb level was increased from 11.7 ± 2.47 gm/dl to reach 13.06 ± 1.6 gm/dl. This is due to decreased or absent bleeding episodes [21],& decreased platelets count from 357 ± 119.53 to 300 ± 76.34 with p- value was significant 0.005, while WBC and its differential count were not affected. Platelets was decreased because of reduced bleeding, no iron deficiency anemia which is associated with higher platelets count[22]. There were no statistically significant changes in the renal& liver function tests, this is similar to European medical agency [23], while apposite to the study done in Japan [24].

The proportion of patients in this study on emicizumab were reported to develop skin reaction (28.12%), itching at the site of injection was the commonest adverse effects was seen in 18.75. This was compatible to

Oldenburg J, et al [13] , where the injection site reaction was found in 20-32%, but against Young G et al[25]whoshowed the most common adverse event were nasopharyngitis. In the current study rash, headache &fever were demonstrated in 9.37%, 9.37% and 3.12%,respectively. All these adverse effects resolve spontaneously with no need treatment. We had no evidence of thrombosis, nasopharyngitis or tonsillitis.

5. CONCLUSION

emicizumab prophylaxis therapy every 4 weeks, in HAI adult &pediatric patients, is safe, effective, improve quality of life & cost effective.

6. ACKNOWLEDGMENTS

The authors thank all the patients, their families, all investigators in Iraqi hemophilia centers participated in the study.
NK, designed and planned the study, NK,OS,AS,IM,AI and YS collected the data, NK,OS and AS analyzed the data & contributed to the writing of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest: None.
Source of Funding: None.

REFERENCES

[1] Scott JP, Flood VH. Hereditary Clotting Factor Deficiencies. In: Kliegman RM, Nelson WE (eds).Nelsons Textbook of Pediatrics. 21st ed. Philadelphia, USA: Elsevier.2020; 10202-10215.
[2] 2.Carcao M, van denBerg, Gouider E, et al. Prophylaxis in Hemophilia . WFH Guidelines for the Management Hemophilia, 3rd edition. *Haemophilia.* 2020; 26(Suppl 6):72-84.
[3] 3.Miesbach W, Schwäble J, Müller MM,et al. Treatment Options in Hemophilia.DtschArztebl Int. 2019; 116(47): 791–798.
[4] Carroll L, Benson G, Lambert J, et al . Real-world utilities and health-related quality-of life data in hemophilia patients in France and the United Kingdom. Patient Prefer Adherence. 2019 Jun 14; 13:941–957.https://doi.org/10.2147/PPA.S202773.
[5] Xu RH, Dong D, Luo N, et al. Investigating the Added Value of the EQ-5D-5L With Two Bolt-On Items in Patients With Hemophilia. Front. Med. August 2021; 8:707998. Doi: 10.3389 / fmed. 2021.707998.
[6] 6.Beeton k, de Kleijn P, Hilliard P, et al. Recent developments in clinimetric instruments. Haemophilia. 2006; 12(Suppl. 3): 102–107.
[7] Brooks R, Boye KS, Slaap B. EQ-5 D: a plea for accurate nomenclature. J Patient Reported- Outcomes4. 2020; 52:1-3.https://doi.org/10.1186/s41687-020-00222-9.
[8] Hassan TH, Badr MA, Fattah NRA, et al. Assessment of musculoskeletal function and mood in hemophilia A adolescents: Across–sectional study. Hemophilia .2011 Jul; 17(4):683-688.
[9] Roberts HR, Monreo DM, White GC. The use of rFVIIa in the treatment of bleeding disorder. Blood.15, 2004; 104(13): 3858-3864.
[10] Hemlibra prescribing information. http: //www . gene.com. Revised 10/2018.
[11] 11.Quellec SL. Clinical Evidence and Safety Profile of Emicizumab for the Management of Children with Hemophilia A . Drug Des DevelTher. 2020 Feb 3; 14:469-481. doi: 10.2147/DDDT.S167731.
[12] 12.Registry Report on Males with Hemophilia 2014-2017. https://www.cdc.gov/ncbddd/hemophilia/communitycounts/registry-report-males/index.html. last reviewed: December 2, 2021.
[13] 13.Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab Prophylaxis in Hemophilia A with inhibitors.N EnglJMed . 2017 Aug 31; 377 (9):809-818.
[14] 14. Rind D, Agboola F, Kumar V et al. Emicizumab for HAI : Effectiveness and value . Institute for clinical and Economic Review (final evidence report). https: // icer . org/wp- content /uploads/2020/10/ICER _ Hemophilia _Final_Evidence_Report_041618.2018 April 16:1-162.
[15] 15.Barg AA, Avishai E, Budnik I, et al . Emicizumab prophylaxis among infants and toddlers with severe HAI-a single-center cohort.Pediatr Blood Cancer. 2019 Nov; 66(11):e27886.
[16] 16. Oldenburg J, Mahlangu JN, Bujan W, et al. The effect of emicizumab prophylaxis on health-related outcomes in persons with HAI: HAVEN1 study. Haemophilia .2019 Jan; 25 (1):33-44.

[17] 17.Lee H, Cho H, Han JW, et al. Cost-utility analysis of emicizumab prophylaxis in haemophilia A patients with factor VIII inhibitor in Korea. Haemophila .2021 Jan; 27(1):12-21.
[18] 18.Bowyer A, Kitchen S, Maclean R. Effects of emicizumab on APTT, one-stage and chromogenic assays of factor VIII in artificially spiked plasma and in samples from haemophilia A patients with inhibitors. Haemophilia .2020; 26(3):536-542.
[19] 19.Nougier C, Jeanpierre E, Ternisien C, et al. Emicizumab treatment: Impact on coagulation tests and biological monitoring of haemostasis according to clinical situations (BIMHO group proposal). European journal of Haematology .2020 Dec; 105(6):p675-681.
[20] 20.Lenting PJ. Laboratory monitoring of hemophilia A treatments: new challenges. Blood advances.2020 May; 4(9):2111-2118.
[21] 21.Poongavanam P, Nandakumaran J, Shanmugam M, et al. The frequency of iron deficiency among patients with hemophilia. IOSR Journal of Dental and Medical Sciences (IOSRJDMS) .2017; 16: 04-9.
[22] 22.Mhadgut H,Galadima H,Tahhan HR. Thrombocytosis in Iron Deficiency Anemia. Blood 2018 Dec 29; 132 (supplement 1):4985-4985.
[23] 23. European Medicines Agency. Assessment report pdf, Hemlibra.https://www.ema.europa.eu/. 25 Jan 2018:1-126.
[24] 24.Shima M , Hanabusa H , Taki M ,et al. Long -term safety and efficacy of emicizumab in a phase 1/2 study in patients with hemophilia A with or without inhibitors .Blood adv. 2017 Sep 27; 1(22): 1891-1899.
[25] 25. Young G, Liesner R, ChangT, et al. A multicenter, open-label phase 3study of emicizumab prophylaxis in children with hemophilia A with inhibitors.Blood.2019; 134(24):2127-3183.

Table 1: Demographic distribution of the cases(No.32)

Item		Number	%	Mean ±SD
Age	≤ 6 years	9	28.12)(	16.07±12.32
	>6 -≤12 years	9	(28.12)	
	>12-≤18 years	6	18.76)(	
	>18 years	8	25)(	
Body Weight	≤20 kg	11	34.38)(	40.09± 25.77
	>20-≤40 kg	8	25)(	
	>40 kg	13	40.62)(	
Inhibitor Level (Bethesda unit)	≥5-≤10 BU	16	50)(	20.187± 20.01
	>10-≤20 BU	10	31.25)(	
	>20 BU	6	18.75)(	
FVIII Level	<1%	26	81.25)(	0.66± 0.35
	≥1-≤5%	6	18.75)(	
Infection Screen	HCV	5	15.62)(	-
	HBV	1	3.12)(	
	HIV	0.0	0.0)(	

Table 2: Distribution of cases according to variable factors of severity of disease, degree of arthropathy and quality of life .

Variable Factors		Pre-Emicizumab (on rFVIIa treatment) Mean ±SD	At 6 months of Emicizumab treatment Mean ±SD	P-value
Bleeding Rate	Bleeding attacks	30.5 ± 7.77	1.5 ± 0.707	0.01
	Joints bleeding	13.43 ± 10.02	0.93 ± 0.39	0.000
Number of hospital Admissions		2.87 ± 5.001	0.000	0.003

Blood transfusion times	1.34 ± 3.03	0.000	0.018
School or work absence days	50.87 ± 43.4	0.00	0.000
FISH Score	21.29 ± 5.44	28.88 ± 3.08	0.000
EuroQol 5-dimention5-level (EQ-5D-5L)	22233	11112	0.05

Table 3: Distribution of cases according to mean level of laboratory finding before &after Emicizumab prophylaxis

Variable factor			6 months of rFVIIa therapy : mean ± SD	6 months of Emicizumab therapy: mean±SD	P-value
APTT			92.76 ± 11.15	28.24 ± 5.46	0.000
Complete Blood Count	WBC	Total	7.36 ± 2.30	7.27 ± 1.99	0.801
		Neutrophils %	48.32 ± 10.72	46.89 ± 14.03	0.59
		Lymphocyte%	39.64 ± 10.52	42.48 ± 13.06	0.32
	Hb%		11.7 ± 2.47	13.06 ± 1.6	0.005
	Platelet count		357.7 ± 119.53	300 ± 76.34	0.005
Liver Function		TSB	0.57 ± 0.33	0.63 ± 0.35	0.49
		ALT	21.7 ± 89	24.06 ± 9.11	0.25
		AST	24.68 ± 13.39	24.18 ± 8.73	0.85
		ALK	174.08 ±50.8	191.5 ± 70.74	0.48
Renal Function		Blood urea	22.15 ± 7.19	24.6 ± 9.41	0.13
		S. creatinine	0.54 ± 0.20	0.55 ± 0.16	0.77