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Research Article

Emicizumab Therapy for Hemophilia Persons; Pilot study; non-Intentional Delay of Maintenance Doses

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Abstract

The emicizumab represent the first non- factor replacement therapy, which is new treatment not require for intravenous access and used for patient with hemophilia A and the information's from 3 phases demonstrated that emicizumab is safe and effective and improved the life style for person with hemophilia A. This drug represents the first non- factor replacement therapy, which is new treatment not require for intravenous access and used for patient with hemophilia A and the information's from 3 phases demonstrated that emicizumab is safe and effective and improved the life style for person with hemophilia A. The objective of this papers to assess and evaluate bleeding episode for patients with delayed maintenance monthly doses of emicizumab. This study for small group Iraqi patients with severe hemophilia A with and without inhibitors exposed for non-intentional delayed for maintenance doses of emicizumab for seven months. The questionnaire included full general information's about the age, weight, inhibitor status and other clinical details about general condition before and after initiation of emicizumab therapy. All patients age enrolled in this study were above 20 years old with a median age of at initiation of therapy and their weight more than 50 kilograms and most of them are hemophilia with inhibitor's changed from factor VII therapy to emicizumab. Most of them exposed to different period maintenance treatment delayed for more than two weeks without any bleeding episodes. In conclusions this study shows delayed monthly maintenance dose of emicizumab dose without bleeding episodes. But because of small groups of patients were studied, so this cannot be regarded a standard treatment for all the patients. I recommend to use more data and large patients' number with same period or emicizumab maintenance dose given every six weeks instead of four weeks.

Key words: emicizumab; maintenance treatment

Introduction

Treatment of the hemophilia an evolving in the last few decades from blood product with plasma-derived to recombinant factors replacement therapy [1]. However, patients on factor replacement therapy have different problems related to the requirement for intravenous access to administer factors and development of immunogenicity of replacement FVIII clotting factor pharmacokinetics (PK) characterized by peaks and troughs, with the latter associated with breakthrough bleeding [2]. The first non- factor replacement therapy is emicizumab which is new treatment not require for intravenous access and used for patient with hemophilia A with inhibitors developed to address these unmet needs, and the first non-factor therapeutic licensed. Emicizumab is a bispecific monoclonal antibody lead to activation both Factor IX and Factor X and restore the hemostatic function of the absent Factor FVIII in hemophilia A patient [3]. It is used to prevent bleeds in person with hemophilia A with and without inhibitors. Data from four Phase 3 studies (HAVEN 1, HAVEN 2, HAVEN 3 and HAVEN 4) demonstrated that emicizumab is safe and effective and improved the life style for person with hemophilia A [4]. The safety of emicizumab had been documented in multiple clinical trials over all the world for patients with hemophilia A with and without inhibitors [5-6]. Most of the studies shows emicizumab safety in different clinical trials. Anti-emicizumab antibodies have been reported in very few cases [7]. but the overall immunogenicity is very low after emicizumab therapy if compares with factor replacement treatments [8]. With using emicizumab breakthrough bleeding may occurs but no side effect seen with usage of diverse replacement therapies [9].

Patients and Methods

This is a retrospective meta-analysis study for seven patients in which clinical data were collected for seven months (9/8/2022 through 9/2/2023) of irregular treatments from medical records. This study for seven Iraqi patients with severe hemophilia A with and without inhibitors exposed for non-intentional delayed for maintenance doses of emicizumab for seven months. The questionnaire included full general information's about the age, weight, inhibitor status and other clinical details about general condition before and after initiation of emicizumab therapy.

Results

Table 1 shows the patients details with their clinical information's and inhibitors concentrations. All seven patients age above 20 years old with a median age of 33.2 years (range 22-50 years) at initiation of therapy and their weight more than 50 years' average weight equal to 71.14 kilogram. Table - 2 shows different period treatment delayed with verage delayed in treatment for patient ID-A (>19 days), patient ID- B (12 days), patient ID-C (14 days), patient ID-D (more 12 days), patient ID-E (> 14 days), patient ID-F (>12 days) and G (> 14 days) respectively with longer period reached to 55 days in patient ID –A.

Patient id	Age of the patient	Body weight	Inhibtor status	Inhibtors titre level	Frequency Dosage delay	Longest duration of delayed	Bleeding episode	Previous treatment before emcizimab
A	50 yrs	72 KG	positive	Over 8	6 times	55 days	0	FVII
B	22 yrs	50 KG	negative	Not known	6 times	26 days	0	FVIII
C	44 yrs	83 KG	positive	64	6 times	35 days	0	FVII
D	25 yrs	78 KG	positive	OVER 5	6 times	20 days	0	FVII
E	31 yrs	74 KG	positive	OVER 10	6 times	29 days	0	FVII
F	38 yrs	81 KG	positive	6	6 times	26 days	0	FVII
G	23 years	60 KG	positive	12	6 times	33 days	0	FVII

Table-1: General Informations of The Patients for Pateints with Hemophilia

Patients ID	Durations of delayed dose for each month (in days)							Bleeding Episoes with Each Dekay
A	14 days	9 days	55 days	10 days	7 days	35 days	4 days	0
B	14	11	26	9	7	15	4	0
C	12	11	35	12	8	17	3	0
D	11	13	20	5	14	14	7	0
E	16	16	29	10	14	9	5	0
F	15	10	26	11	12	11	4	0
G	13	8	33	11	10	14	10	0

Table-2: Represent The Duration Delay of Maintaince Emicizumab with Each Month

Discussion

Studies have shown that current treatment with regular IV infusions increase the burden for HA patients, notably in children and adolescents, and their caregivers. It induces financial, technical, and educational challenges that considerably impact their quality of life [10]. This study for a small group study, in which seven Iraqi patients with severe hemophilia A (1 negative for inhibitors but not respond to usual dose of the factor eight replacement therapy and other six patient positive for inhibitors) received once weekly to 4 weekly low dose subcutaneous emicizumab (3 mg/kg/ week) followed by proposed (6 mg/kg/ month) , but delayed of monthly doses occurs in different variable times due to delayed in providing the dose from the store site and with time of intake after participating in the study and were followed by a one-year retrospective. All patients were examined every month to assess bleeding rate and to report events during the time of delayed treatment. monthly bleeding rates and annual joint bleeding rates are estimated. There is no test available for measurement the level of Emicizumab concentrations after infusion during all period of study. The all persons enrolled on this study received the induction loading doses of emicizumab on regular manner, according to the drug guideline information's, is 3 mg/kg subcutaneously, once weekly for the first 4 weeks and then 6 mg/kg monthly [11]. All received the first month doses on the true time but delayed in providing of the drugs from sources occurs from the second month with different time delayed in each months between days' weeks or even more than one months. Two patients had been delay their dosage for more than month while the remaining five patients their treatment delayed equal or more than 3 weeks: Table 1 shows the patients details with their clinical information's and inhibitors concentrations. All seven patients age above 20 years old with a median age of 33.2 years (range 22-50 years) at initiation of therapy and their weight more than 50 years' average weight equal to 71.14 kilogram. The inhibitor levels for the six patients with inhibitors were over 5. however, during these periods we kept the patient on close follow up and didn't used the bypass agents, fortunately no symptoms of bleeding occurred during these periods. All patients received their treatment at hematology center by qualified nurse under doctor supervision. All patients required psychological support and reassurance to overcome the anxiety during the first two months of delayed and we give them advice to decrease the physical activities like walking for long period but these anxieties decrease or not significant in the next five months as theirs no pain, no hospital admissions and no symptoms recorded during delayed treatment period and most of the patients did usual daily activity. Table -2 shows different period treatment delayed with verage delayed in treatment for patient ID-A (>19 days), patient ID- B(12 days), patient ID-C (14 days), patient ID-D(more 12 days), patient ID-E(> 14 days), patient ID-F(>12 days) and G(> 14 days) respectively with longer period reached to 55 days in patient ID –A.The important point of this study explained that there are no bleeding events during reported during the time of non-intentional delayed of medication even in more than one month in patient ID-A, patient ID-C and patient ID-G.

In conclusion, the study of this small group of Iraqi Hemophilia A patients with inhibitors or even without inhibitors shows that even delayed time of monthly emicizumab dose without bleeding episodes. Because of small groups of patients were studied, so this cannot be regarded a standard treatment for all the patients. I recommend to use more data and large patients' number with same period or emicizumab maintenance dose given every six weeks instead of four weeks with normal daily physical activity can result in non-bleeding events and this help in decreasing the cost of drugs prophylaxis and reduced the health care budgets especially in low- or moderate-income countries and give more time for health care administrative for test, store and drug distribution. The safety profile of emicizumab in most center, easiest way of administrations subcutaneously and long intervals for each dose makes patients satisfy and so thankful for this type of treatment.

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Conflict of interest

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent Verbal

Informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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