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Emicizumab: Reshaping Lives

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Abstract

Objective: To determine the effectiveness of Emicizumab in patients with high annual bleeding rate (ABR) and in patients who needed rehabilitation (physical/psychological) along with any side effects.
Methodology: This prospective cohort study was conducted at Hemophilia Patients Welfare Society (HPWS) Lahore Chapter. A total of 37 patients were followed up for a period of 1 year after starting treatment with Emicizumab. Mean annual bleeding rate (ABR) per patient, attendance status at School/college/job, mental health issues, number of hospital visits and Hemophilia joint health society score (HJHS score) in last 2 years prior to the start of therapy were recorded and were then compared with the results 1 year after the start of treatment. Data was analyzed using SPSS version 23.00. Mean and standard deviation were calculated for continuous variables, median and IQR were calculated for discrete data. Frequencies and percentages were calculated for categorical variables. Shapiro-wilk test was used to test the normality of the data. Wilcoxon-signed rank test was used evaluate the difference in ABR and HJHS before and after treatment. A p-value of less than 0.05 was considered as significant.
Results: After start of treatment patients showed 100% improvement in their attendance status. Only 6 patients (16.2%) had major breakthrough bleeds at different sites after start of treatment. The median Hemophilia Joint Health Society Score (HJHS) reduced from 8 (IQR: 8-15) to 7 (IQR: 5.5-14.5) p value = 0.001. The median number of hospital visits per year were 6 (IQR: 2-12) before the start of treatment and after intervention the median number of visits reduced to 0 (IQR: 0-0). The ABR median values before start of treatment were 3.5 (IQR: 0.5-8.25) and after start of treatment the median value reduced to 0 (IQR: 0-0) (p value <0.001).
Conclusion: Emicizumab has a promising role in enhancing the quality of life of hemophiliacs, thereby we strongly suggest the last scale local production and use of Emicizumab.
Key words: Emicizumab, Hemophilia A, Rehabilitation

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Introduction

Hemophilia A (HA) is a congenital X-linked disorder characterized by deficiency of factor VIII deficiency. The severity of symptoms depends upon the degree of factor deficiency. The hallmark of HA is bleeding into joints specially in weight bearing joints like ankles, knees and elbows. Repeated spontaneous or trauma-based bleeds eventually leads to arthropathy. Life-threatening bleeds like intracranial bleed can also occur.[1]. Over the years, progress has been made in the management of hemophilia patients. The aim has always been to give these patients a normal life with minimum episodes of bleeds. Emicizumab is one such innovation which has proved to be effective in remolding the lives of persons with hemophilia A (PwH) with or without inhibitors.[2]

Traditionally, factor replacement either through blood products or recombinant clotting factors are used for prophylaxis or to manage bleeds. However, these modalities lead to complications like development of inhibitors.[3] Emicizumab is a licensed non-factor therapeutic which is used for treatment of HA. It is a monoclonal antibody which binds factors IXa and X, resulting in spatial approximation and activation of factor X, thereby mimicking the actions of factor VIII.[4]

In Pakistan, PwH experience a lot of psychosocial issues. Around one third of the patients experience severe anxiety and depression apart from the physical disability.[5] Treatment centers for HA are only available in major cities of Pakistan which relay on limited lab facilities and have scarcity of recombinant factors. In Pakistan, a more proactive approach is needed due to lack of resources and funding from the local government. Rehabilitation, psychosocial issues and increased usage of on-demand recombinant FVIII are some of the main concerns which are becoming very challenging. Therefore, a need arises for a sagacious line of action where Emicizumab could also be used in patients who need grueling physiotherapy and psychosocial rehabilitation.

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Conflict of Interest: none

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Methodology

This prospective cohort study was conducted at Hemophilia Patients Welfare Society (Lahore Chapter) in order to evaluate the effectiveness of Emicizumab in patients with HA who have been under treatment with this drug for at least 1 year.

Patients with Hemophilia A who were registered at HPWS Lahore and have been under treatment with Emicizumab for at least 1 year were included whereas all other Hemophilia A patients were excluded from the study.

According to recent data, the World Federation of Hemophilia (WFH) reported that 195,263 patients from 115 countries were diagnosed with hemophilia in 2019, of which 2233 patients were identified from Pakistan(6). Given the small population of registered patients with hemophilia in Pakistan we decided to include in our study all 37 patients (which fell under our inclusion criteria) with HA registered in Hemophilia Patients Welfare Society (Lahore Chapter). Informed written consent was taken from all patients included in the study and their confidentiality was maintained. All 37 patients in our study were followed up for a period of 1 year after starting treatment with Emicizumab. Mean annual bleeding rate (ABR) per patient, attendance status at School/College/Job, mental health issues, number of hospital visits and Hemophilia Joint Health Society Score (HJHS score) in last 2 years prior to the start of therapy were recorded and were then compared with the results 1 year after the start of treatment. Number of breakthrough bleeds, use of any additional hemostatic agents and side effects (if any) caused by Emicizumab were also noted. Data was analyzed using Statistical Package for the Social Sciences (SPSS) version 23.00.

Mean and standard deviation were calculated for continuous variables, median and IQR were calculated for discrete data. Frequencies and percentages were calculated for categorical variables. Shapiro-wilk test was used to test the normality of the data. Wilcoxon-signed rank test was used evaluate the difference in ABR and HJHS before and after treatment. A p-value of less than 0.05 was considered as significant.

Results

The mean age of the 37 male patients included in our study was 16.76 ± 10.57 years. 13 (35.1%) out of these were college students while 7 (18.9%) belonged to pre-school children category and 7 (18.9%) to high school children category. 2 (5.4%) patients were underage for school and 6 (16.2%) patients had already graduated from college/university. Out of 37, 3 (8.1%) patients used additional hemostatic agents while on treatment with Emicizumab. This included use of Kovate 500 IU and Eloctate 500 IU in one patient, Kovaltry 1000 IU in second patient and Ayro seven in the third patient. Nine patients (24.3%) experienced some side effects while using Emicizumab. The most frequent side effect observed was headache in 5 (13.5%) patients. 3 (8.1%) patients experienced nausea and 1 (2.7%) had frequent episodes of fever with its use, however, none of these side effects were severe enough to warrant discontinuation of treatment. Fifteen (40.5%) patients out of 37 had different mental health issues before start of treatment with Emicizumab. Out of these 15 patients 13 (86.6%) patients had improvement in their mental health status while 2 (13.4 %) didn't show any improvement. (Table I).

Table I: Mental health status before and after Emicizumab use.

Mental health issue before Emicizumab use	No. of patients (n=37)	Patients with improvement	Patients without improvement
Anxiety	4 (10.8%)	4 out of 4(100%)	Nil
Depression	4 (10.8%)	3 out of 4(75%)	1(25%)
Both anxiety and depression	6 (16.2%)	5 out of 6 (83.3%)	1(16.7%)
Fainting spells	1 (2.7%)	1 out of 1 (100%)	Nil
None	22 (59.5%)	-	-

The median number of hospital visits per year were 6 (IQR: 2-12) before the start of treatment and after intervention the median number of visits reduced to 0 (IQR: 0-0). Out of 37 patients 2 (5.4%) had occasional absences from school/ work before treatment and 24 (64.9%) had long term absences from school/ work. 6 (16.2%) patients were regular even before start of treatment while 5 (13.5%) were not in school/ office going category. After start of treatment both categories of patients (those with occasional absences and long-term absences) showed 100% improvement in their attendance status and became regular. 6 patients (16.2%) had major breakthrough bleeds at different sites after start of treatment (Table II). The median and mean of average ABR of patients 2 yrs prior to start of treatment and 1 year after start of treatment was

calculated. The median values before start of treatment were 3.5 (IQR: 0.5-8.25) and after start of treatment the median value reduced to 0 (IQR: 0-0) (p value <0.001). The median Hemophilia Joint Health Society Score (HJHS) reduced from 8 (IQR: 8-15) to 7 (IQR: 5.5-14.5) p value = 0.001 (Table II; Figure 1). Results of different parameters before and after treatment are summarized in Table III.

Table II: Break through bleeds in patients on Emicizumab.

Type of break through bleed	Frequency
No breakthrough bleed	84%
Post-traumatic bleed	8%
Joint bleed	5%
Mucosal bleed	3%

Table III: Effect of Emicizumab on different parameters in patients with haemophilia A.

Parameter	Before Emicizumab	After Emicizumab	*p* value
Median hospital visits per year	6 (IQR: 6-12)	0 (IQR: 0-0)	-
No. of patients with attendance issues	26 (70.2%)	0 (0%)	-
Median ABR	3.5 (IQR: 0.5-8.25)	0 (IQR: 0-0)	<0.001
Mean ABR	5.38 ± 6.56	0.49 ± 2	-
Median HJHS	8 (IQR: 8-15)	7 (IQR: 5.5-14.5)	0.001
Mean HJHS	10.89 ± 9.14	9.3 ± 6.98	-

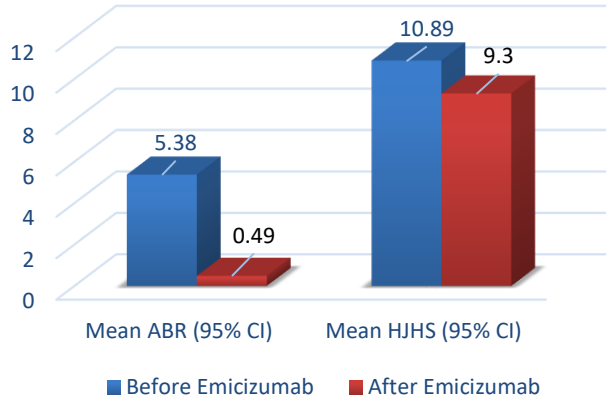

Figure I. Mean ABR and HJHS before and after treatment with Emicizumab.

Discussion

Emicizumab is considered a safe drug however side effects are often observed. According to Gelbenneger et al, injection-site reactions are the most common side effects followed by headache (15%), arthralgia (15%), pyrexia (6%), and diarrhea (6%).[7] The most common adverse effect observed in our study was headache experienced by 13.5% patients. Only 8.1% patient had nausea and 2.7% experienced pyrexia. None of the severe adverse effects like ST-segment elevation myocardial infarction and pulmonary embolism, lupus nephritis or rhabdomyolysis were reported in our study. [8]

The median Hemophilia Joint Health Society Score (HJHS) was reduced from 8 (IQR: 8-15) to 7 (IQR: 5.5-14.5) in our study. Similar findings were observed in Karachi where HJHS was significantly improved after treatment with Emicizumab. Likewise, anxiety/depression also improved 58.6% patients under treatment in Karachi whereas 86% patients showed improvement in their mental health in our setup.[9]

In our study group ABR was drastically improved after the use of Emicizumab. This had direct impact on the quality of life of the hemophiliacs as this improved their daily performance at school or work. Our study showed 100% improvement in daily attendance of patient in their study/work. Similar observations were made by Buckner et all who observed that HRQoL (health related quality of life) in HA on Emicizumab, as measured by PROMIS-29 domain T-scores, generally did not differ from that of the US reference population apart from some pain interferences.[10] Skinner et al also showed that use of Emicizumab improved the HRQoL and caused less disruption of work when compared to previous treatment modalities.[11]

Limitation of the Study: Study was was conducted on 37 patients due to lack of funding and limited availability of Emicizumab.

Conclusion

Emicizumab has showed good safety and tolerability in our study population with significant and important improvements in terms of bleeding and quality of life. Overall, the use of Emicizumab can benefit patients with HA as it can solve issues like joint deformities, mental health problems and generalized wellbeing. Emicizumab has a promising role in enhancing the quality of life of PwH thereby we strongly suggest the last scale local production and use of Emicizumabin order to give a better fighting chance to patients with HA and would further reduce economic burden on the health sector of

the country as fewer complications would require less money being spent on an individual patient.

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