CLINICAL EFFICACY OF RECOMBINANT FACTOR VIII FC FUSION PROTEIN IN HAEMOPHILIA A PATIENT RECEIVING ON DEMAND TREATMENT ONLY

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ABSTRACT

Objective: To evaluate the efficacy of recombinant factor VIII FC fusion protein in haemophilia A patient receiving on demand treatment only.

Study Design: Comparative cross sectional study.

Place and Duration of Study: Department of Hematology, Armed Forces Institute of Pathology and Pakistan Hemophilia Welfare Society, Rawalpindi, from Jun to Dec 2017.

Methodology: Eighty-nine male patients of Hemophilia A already receiving recombinant factor VIII (20-30 Units/kg) on demand, with no history of inhibitors were included in study. Patients were divided as per age into paediatric and adult group and also on the basis of their basal factor VIII levels into severe, moderate and mild groups. Same patients were switched to recombinant factor VIII FC fusion protein (20-30 Units/kg) and its efficacy was measured and compared with recombinant Factor VIII in terms of dose requirement, injections, bleeds in six month period, presence of inhibitors and side effects.

Results: Eighty nine male patients were studied. There was significant reduction in dose from median value of 5750 units for group I to 4000 units for group II. Number of bleed in six month period were reduced from 5.3 in group I to 4.5 in group II. Number of injections were reduced on average to 1-2 injection per bleed in group II. No inhibitors were detected in group II.

Conclusion: rFVIII Fc fusion protein has prolong activity and results in reduction of total dose, number of bleed, dose per bleed and has reduced antigenecity.

Keywords: Hemophilia A, Recombinant factor VIII, Recombinant factor VIII Fc fusion protein.

INTRODUCTION

Hemophilia A is X linked recessive inherited disease cause by deficiency of coagulation factor VIII (FVIII)[1]. It is characterized by bleeding into joints, muscles and body cavities such as CNS[2]. When inadequately treated, this leads to chronic arthropathy, disability and increased risk of death[3]. Bleeding may be spontaneous or traumatic. Patients with severe hemophilia A (factor level <1%) typically present with spontaneous bleeding typically into joints and muscles, whereas patients with moderate disease (factor level 1-5%) or mild disease (factor level 5-50%) only be diagnosed later in life following a haemostatic challenge[4,5].

The mainstay of treatment for individuals with severe hemophilia A is replacement therapy with coagulation factor VIII[6]. According to world hemophilia federation different treatment protocols are available which include prophylactic treatment (given twice or thrice weekly) and on demand therapy which is given when patient present with a bleeding episode[7]. Recombinant factor VIII (rFVIII) products have been available as replacement therapy in hemophilia A since 1990s[8]. However conventional FVIII products which have half life of 12 hours, require frequent intravenous infusion of replacement factor to maintain protective FVIII levels above 1%[9,10].

Recombinant factor VIII Fc Fusion molecule is composed of a single molecule of B-domain deleted recombinant factor VIII (rFVIII) covalently fused to the dimeric Fc domain of IgG1 which binds the neonatal Fc receptor, and utilizes the IgG recycling pathway to extend plasma half life[3,10]. Recombinant FVIII Fc fusion protein has approximately 1.5 fold longer half life than rFVIII

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and overall improve management and quality of life of Hemophilia A patients[10].

In this study we compare clinical efficacy of recombinant factor VIII to recombinant factor VIII Fc fusion protein which has extended half life of 19 hours and less antigenic.

METHODOLOGY

This was comparative cross sectional study conducted at Armed forces institute of Pathology and Pakistan society of Hemophilia Islamabad/ Rawalpindi from June 2017 to December 2017 using nonprobability Consecutive sampling technique. The protocol was approved by the local institutional review boards (FC.HEM 16-,12/ READ-IRB/1 7 1286). Written informed consent was obtained from the patients.

Sample size was calculated using WHO calculator for sample size. Eighty nine patients who were diagnosed cases of hemophilia A, aged above 3 years with no history of co-morbid and inhibitors to factor VIII and were receiving rFVIII for at least last six months, were included in study. Exclusion criteria include patients below 3 years of age, presence of inhibitors to factor VIII, any co-morbids, and known hemophiliacs undergoing surgical treatment. To avoid any change in genetic makeup same patients who were receiving recombinant factor VIII for at least 06 six month were switched to recombinant factor VIII Fc fusion protein.

Patients were divided into different groups according to age and severity of disease. As per age patients were divided into 2 groups. Group A below and equal to 12 years (n=44%) and Group B included patients above 12 years (n=56%). According to severity as per WHO classification patients were further divided into mild (n=09), moderate (n=40) and severe group (n=40). All groups were compared in terms of number of bleeds, number of injections required per bleed, dose per bleed, total dose and side effects in six month period.

Patients' previous data with recombinant factor VIII at dose of 20-30 IU/kg had been analyzed for number of bleeds, number of injections, dose required /bleed and total dose in 6 months. Same patients had been switched to rFVIII Fc fusion protein at dose of 20-30 iu/kg and followed for six months for number of bleeds, injections per bleed, dose required per bleed and any adverse events. At the end of study individuals were screened for the presence of inhibitors. About 1.8 ml of blood in 0.2ml of tri-sodium citrate was collected in laboratory. Screening was done for both immediate and delayed inhibitors by mixing studies by aPTT method. Data was analyzed using SPSS version 24. Frequency and percentages were calculated for qualitative data, mean ± SD was calculated for quantitative data. Paired sample t test was for comparison of mean difference. A *p*-value ≤0.05 was considered as significant.

RESULTS

A total of 89 male patients were included in this study, mean age of the patients was 16.07 ± (SD=2.2) years, mean age of group A was 8 ± (SD=3) years and group B was 22 ± (SD=3) years. Mean dose of RF VIII in pediatric groups was

Table-I: Comparison of mean difference of both age groups in Recombinant factor VIII and Recombinant factor VIII FC fusion protein.

Age Group	RF VIII Mean ± SD (n=39)	RF VIII FC Mean ± SD (n=50)	*p*-value
Dose			
≤12 Years	4207.69 ± 388.720	3192.31 ± 276.51	0.014
>12 Years	7333.0 ± 417.72	5889.80 ± 338.68	0.023
Injection			
≤12 Years	6.82 ± 0.78	5.23 ± 2.69	0.025
>12 Years	8.60 ± 2.83	6.10 ± 3.43	0.001
Bleeding			
≤12 Years	4.44 ± 2.45	4.13 ± 2.43	0.02
>12 Years	5.29 ± 2.98	4.76 ± 3.54	0.001

4207.69 ± (SD=388.720) IU and in adult group was 7333.0 ± (SD=417.72) IU (*p*=0.014), mean dose of RF VIII FC in pediatric groups was 3192.31 ± (SD=276) IU (*p*=0.014), and in adult group was 5889.80 ± (SD=338.68IU) (*p*=0.023). A significant

reduction in number of injections, bleeding, traumatic and Spontaneous was seen in both age groups, shown in table.

Table-II shows the comparison of RF VIII and RF VIII FC according severity of disease, significant statistical difference in total dose, number of bleeds and injections required in all three groups.

Table-II: Comparison of RF VIII and RF VIII FC fusion protein according severity of disease.

	RF VIII Mean ± SD (n=39)	RF VIII FC Mean ± SD (n=50)	*p*-value
Total Dose in Six Month Period			
Mild	6083.33 ± 5452.92 IU	4888.89 ± 3196.95 IU	0.122
Moderate	5037.50 ± 3376.74 IU	4418.50 ± 3603.71 IU	0.001
Severe	6858.75 ± 4626.35 IU	4956.25 ± 3290.37 IU	0.002
Number of Injections in Six Month Period			
Mild	7.56 ± 5.19	6.56 ± 5.19	0.585
Moderate	6.68 ± 4.053	5.40 ± 3.82	0.014
Severe	9.03 ± 5.42	5.85 ± 2.82	0.001
Bleeding Rate			
Mild	5.67 ± 4.03	5.22 ± 4.02	0.702
Moderate	4.70 ± 2.59	4.28 ± 2.49	0.091
Severe	5.75 ± 2.77	4.53 ± 2.1	0.001

DISCUSSION

Extended half life of recombinant FVIII Fc fusion protein has overall improve management and quality of life of Hemophilia A patients[11]. Various studies have shown the rFVIII fc was well tolerated without serious adverse events related to the drug[12].

Development of alloantibody to the replacement therapy is the most challenging complication[13]. These alloantibody neutralizes the coagulant activity of infused factor FVIII in upto 30% of previously untreated patients with severe hemophilia A, typically during first 50 exposure days to therapeutic products containing the deficient factor VIII[14]. Inhibitor formation is a T-cell response to foreign infused FVIII that renders life saving factor treatment ineffective and results in poorly controlled bleeding with twice the hospitalization and 10 times the cost of non inhibitor patients[15].

In developed countries usually prophylactic treatment is given with regular follow up[16]. But in developing world, where there is lack of health facilities and limited resources on demand treatment is treatment of choice. In this scenario factor products with extended life can lead to not only reduction in number of injection and dosage but also establishment of arthropathy can be reduced.

This study has confirmed the findings of previous studies in Hemophilia A patients in which recombinant FVIII Fc fusion protein has resulted in decrease number of bleeds, injections and total dose. Patients had experienced minimal side effects and no development of inhibitors[8,9].

Development of rFVIII with extended half life improves the management of hemophilia and improves quality of life of patients by reducing the burden of frequent intravenous injections[17]. Moreover, possibility of maintaining high trough levels effectively cover major surgical procedures with few injections and low factor consumption[18]. Although prophylaxis with regular administration of FVIII in order to prevent joint and severe life and limb threatening bleeds is the recommended treatment for patients with severe hemophilia A[16]. But in resource constraint countries like Pakistan only limited data is available about hemophilia A patients. Availability and accessibility to factor VIII, lack of knowledge of disease and scarce resources for diagnosis are main reasons which results in poor patient care and treatment. Prophylaxis is still not possible due to above mentioned reasons. Here on demand treatment is main choice of treatment. Most patients already develop arthropathy before diagnosis and initiation of treatment.

Data regarding recombinant FVIII Fc fusion protein is very scarce for patients receiving on demand treatment only. However results of our study are comparable with other results of episodic arms of treatment with rFVIII Fc fusion protein in multiple studies[3]. The phase I/II trial (NCT 01027377) shows that rFVIII was well tole-

rated without serious adverse events related to the drug. None of the subjects develop inhibitors to the rFVIII Fc fusion protein. Patients in arm 3 receiving rFVIII fc fusion protein at dose of 10-50IU/kg showed significant reduction in annual bleeding rate[3]. Similar results were obtained by Shapiro *et al*, which also showed reduction in annual bleeding rate of zero percent in patient receiving prophylaxis and on demand treatment[5].

This results are comparable with study conducted by Young *et al*[9]. In our study 85% patients require single dose for each bleeding episode which are compare able with 81.0% of subjects receiving single dose per bleed in study conducted by young *et al*[9]. Bleeding episodes of 75% patients were controlled with single injection which are comparable with our results[3]. Similar results were obtained in A-LONG study by Shapiro *et al*, in his study 98% patients required single dose for treatment of bleeding episode[5].

Annual bleeding rate is reduced in patients receiving rFVIIIFc fusion protein in all groups and these results are comparable with studies conducted by Young at al where while receiving prophylaxis with rFVIII Fc fusion protein ABR were reduced to zero, and Shapiro *et al* and Berntorpal[5,8-10].

The most challenging complication of replacement therapy is the occurrence of alloantibodies that neutralizes factor VIII in upto 30% patients receiving rFVIII[4,7,9,11]. Inhibitors compromise the ability to manage hemorrhage, which results in increased morbidity and disability for patients and cost[9]. Risk factors for development of inhibitors can be related to patient (i.e; age of patient, race, positive family history, and factor VIII genotype) or can be related to treatment (i.e; high intensity treatment at young age)[7]. In our study 40 patients had been evaluated for presence of inhibitors at the end of study, none of them had developed inhibitors which confirms the low immunogenicity of rFVIII Fc fusion protein as shown in other studies. No inhibitors were detected in study conducted by Young's *et al* in Children's Hospital Los Angeles, University of Southern California and Berntorp *et al*[9,10].

CONCLUSION

rFVIII Fc Fusion Protein has prolonged half life which results in significant dose reduction and number of injections. It is a better option for patients receiving on demand treatment from far flung and resource constrained areas. However on demand treatment has no effect on arthopathy once it is established. Low dose prophylaxis with long acting Fc Fusion protein can be a choice to reduce hemophilia induced arthopathy.

CONFLICT OF INTEREST

The study has no conflict of interest to declare by any author.

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