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Efficacy & safety profile of Emicizumab in Management of Hemophilia - A Study at a Tertiary care center

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ABSTRACT

Introduction: The conventional treatment of Hemophilia A is based on administration of recombinant/plasma derived factor VIII concentrate. Long term prophylactic treatment with factor VIII concentrates helps in preventing life threatening bleeds but the need for frequent (twice weekly) intravenous administration of factor VIII imposes significant burden on patient affecting their quality of life. Intravenous access is difficult in very young patients. Furthermore 25-40 % of patients with severe Hemophilia develop inhibitors against factor VIII after few courses of replacement therapy. Development of inhibitors is associated with higher rate of bleeding, more disability and decreased quality of life. Administration of bypassing agents like activated Prothrombin complex concentrates(aPCC) or recombinant activated factor VII (rFVIIa) is required to control bleeding in those with inhibitors. Both of them are very expensive.

Materials and methods: The study was started after taking approval from Institutional Ethics Committee. About 20-25 Hemophilia A patients are registered and regularly come for on-demand replacement therapy with factor VIII to this center. Among those, patients of severe Hemophilia A (factor VIII<1%) with frequent & severe forms of bleeds with or without inhibitors were selected for emicizumab therapy. Written informed consent was taken from the parents of patients. Parents were explained about the drug, its cost and the importance of compliance.

Results: Patient 1: An 8-year-old patient was diagnosed to have severe Hemophilia A at the age of 5 years when he had uncontrolled bleeding following dental extraction. He had recurrent joint bleeds and received factor VIII replacement on demand 25 times over a period of one and half years (Baseline ABR of 18 before starting emicizumab). Emicizumab was started in May 2024. After starting emicizumab therapy there were no joint bleeds. There is 5 months gap of emicizumab due to shortage of supply from Government. During this period, he had joint bleeds 2 times (ABR of 4). The drug was restarted and continued till now with no further bleeds.

Conclusion: Emicizumab is found to be game changer in the management of severe Hemophilia A with or without inhibitors. It helped in reversing the preexisting joint morbidity.

Keywords: *Hemophilia A, Emicizumab, Severe Hemophilia A, Annualized Bleeding Rate (ABR), Factor VIII Inhibitors.*

INTRODUCTION

Hemophilia A is a genetic disease characterized by deficiency of clotting factor VIII which is inherited X-linked recessively. Severe form (factor levels <1%) can lead to spontaneous and prolonged bleeding which can be fatal sometimes.

Musculoskeletal bleeding can lead to debilitating chronic disease such as hemophilic arthropathy [1]. India accounts for the largest proportion (12%) of the global population of people with Hemophilia (PWH) [2].

The conventional treatment of Hemophilia A is based on administration of recombinant/plasma derived factor VIII concentrate. Long term prophylactic treatment with factor VIII concentrates helps in preventing life threatening bleeds but the need for frequent (twice weekly) intravenous administration of factor VIII imposes significant burden on patient affecting their quality of life. Intravenous access is difficult in very young patients. Furthermore 25-40 % of patients with severe Hemophilia develop inhibitors against factor VIII after few courses of replacement therapy. Development of inhibitors is associated with higher rate of bleeding, more disability and decreased quality of life. Administration of bypassing agents like activated Prothrombin complex concentrates(aPCC) or recombinant activated factor VII (rFVIIa) is required to control bleeding in those with inhibitors. Both of them are very expensive.

Introduction of the recombinant, humanized bispecific F VIII – mimetic procoagulant antibody emicizumab which can be administered subcutaneously once in 2-4 weeks changed the quality of life in many hemophiliacs. Emicizumab binds to factor IX a and X and activates the later. HAVEN clinical trials (1 to 7) with emicizumab on patients with severe Hemophilia A with or without inhibitors in adults, adolescents, children and infants lead to approval of the drug. US FDA approved emicizumab on November 16th 2017.

Dosage& Adverse effects & Cost of Therapy :
A subcutaneous loading dose of 3mg/kg weekly is given for 4 weeks followed by 1.5mg/kg weekly or 3mg/kg once in 2 weeks or 6mg/kg once in 4 weeks as maintenance[3]. Erythema, pain and pruritis at the injection site are most commonly reported side effects of the drug. The most concerning adverse event with emicizumab was thromboembolic events and thrombotic microangiopathy especially in adults and those who receive aPCC(activated prothrombin complex concentrates) for breakthrough bleeding. Hence the preferred treatment for breakthrough bleeding in patients with inhibitors and receiving emicizumab include infusion of rFVIIa [3].

Cost is the major barrier for widespread use of emicizumab. For a 20kg child the approximate annual cost for maintenance is 7 lakhs.

As per the Annual Global Survey (AGS) from World Federation of Hemophilia for 2022, 607 patients with inhibitor positive Hemophilia are reported from India [4]. Around 93 countries out of 125 countries that submitted data to the AGS have reported usage of emicizumab.

Emicizumab has been available in India since April 2019, initially through direct purchase and now largely through state Government supply. The state of Kerala started providing emicizumab prophylaxis to all children (0-18yrs) with hemophilia who are native to the state [5]. State of UP has been providing treatment with emicizumab since 2020 in 5 centers for Hemophilia. Andhra Pradesh state government started providing emicizumab to Government hospitals from April 2024. Hence this study is taken up to evaluate the efficacy of emicizumab in patients with severe Hemophilia A with or without inhibitors. Its safety profile, patient satisfaction and improvement in quality of life are also evaluated. This is the 1st reported study on emicizumab in government sector in Andhra Pradesh state.

MATERIALS AND METHODS:
The study was started after taking approval from Institutional Ethics Committee. About 20-25 Hemophilia A patients are registered and regularly come for on-demand replacement therapy with factor VIII to this center. Among those, patients of severe Hemophilia A (factor VIII<1%) with frequent & severe forms of bleeds with or without inhibitors were selected for emicizumab therapy. Written informed consent was taken from the parents of patients. Parents were explained about the drug, its cost and the importance of compliance.

Emicizumab was supplied by state Government and all patients received it free of cost.
Based on the quantity of stock available emicizumab was initially started for 3 patients with severe & frequent bleeds in May 2024. Patients received loading dose of 3mg/kg weekly for 4 weeks followed by 3mg/kg once in 2 weeks or 6mg/kg once in 4 weeks thereafter depending on feasibility. The dose was rounded off to nearest vial size whenever possible.
Based on increased availability of drug, 3 more patients were switched over from on-demand factor VIII therapy to emicizumab in July 2025.

Annualized Bleeding Rate (ABR) was calculated at baseline and at 6 months intervals. ABR was defined as the sum of bleeds observed during study period which was annualized.

RESULTS:
Patient 1: An 8-year-old patient was diagnosed to have severe Hemophilia A at the age of 5 years when he had uncontrolled bleeding following dental extraction. He had recurrent joint bleeds and received factor VIII replacement on demand 25 times over a period of one and half years (Baseline ABR of 18 before starting emicizumab). Emicizumab was started in

May 2024. After starting emicizumab therapy there were no joint bleeds. There is 5 months gap of emicizumab due to shortage of supply from Government. During this period, he had joint bleeds 2 times (ABR of 4). The drug was restarted and continued till now with no further bleeds.

Patient 2: A 7 years old patient had uncontrolled bleed following injury to buccal mucosa at 10 months age. His grandfather was a known Hemophiliac. The child was diagnosed to have severe hemophilia A. Since then the child had recurrent joint bleeds involving elbows and knees. Received factor VIII replacement therapy more than 33 times (Base line ABR 8-10). He was started on emicizumab in May 2024 (at the age of 5 yrs). Due to shortage of supply of emicizumab child did not receive it for 5 months. During this period, he had joint bleeds 2 times (ABR of 4). Drug was restarted and continued till now with no further bleeds.

Patient 3: A 6 years old child diagnosed to have Hemophilia at 2 1/2 years age when he had left knee joint bleed following a fall. He had recurrent joint bleeds requiring factor VIII replacement therapy (10-15 per year). He was started on emicizumab in May 2024. He is the only child with moderate Hemophilia A (factor VIII levels 2%) in this study. He maintained zero bleed status for 3-5 months of stopping emicizumab (due to shortage of supply).

Patient 4: A 12 years old child diagnosed to have severe hemophilia A at the age of 3 yrs when he had uncontrolled bleeding after tongue bite. He had recurrent right knee joint bleeds 20 times and developed chronic arthropathy and dynamic contractures of joint. He was tested positive for inhibitors and used to respond to high dose of factor VIII replacement. He was started on emicizumab in July 2025. Since then there were no further bleeds, knee joint swelling subsided and contractures were relieved.

Patient 5: A 9 years old child diagnosed to have severe Hemophilia A at 3 months of age, when he had bruise on the face. He had recurrent bleeds in right elbow and right knee (Target joints) for which he received factor VIII replacement for over 50 times. He was tested positive for inhibitors and was given recombinant factor VIIa to control bleeding. He was started on emicizumab in July 2025.Since then he had no further bleeds.

Patient 6: A 2 years old boy diagnosed to have severe Hemophilia A at 9 months of age when he had uncontrolled bleeding following a fall and injury to buccal mucosa. Since then the child had recurrent elbow & knee joint swellings. Received factor VIII 33 times (ABR 26). This patient was started on emicizumab in October 2025 and there is zero bleed rate now.
Few notable observations:

All doses of emicizumab were administered in hospital and no adverse drug reactions were noted. ABR reduced to zero in all patients during therapy. Even during 5 months gap in therapy (due to shortage of supply) the ABR was 4 compared to baseline of 12-26 in two patients. Patients continued to attend school regularly and the parent / patient satisfaction is very high.

S No	Age of the Child	Age at Diagnosis	First Bleed	Initiation of Emicizumab Therapy	ABR (Before Emicizumab)	ABR (After Emicizumab)	Breakthrough bleeds
Pt-1 (Severe HA)	8 years	5 years	Dental Extraction	May 2024	18	4	2 episodes of joint bleeds during shortage of Emicizumab
Pt-2 (Severe HA)	7 years	10 months	Buccal Mucosa	May 2024	8-10	4	2 episodes of joint bleeds during shortage of Emicizumab
Pt-3 (Moderate HA Factor levels 2%)	6 years	2.5 years	Joint bleed (left knee)	May 2024	10-15	0	No Breakthrough bleeds noted even when not received emicizumab due to shortage of supply

Pt-4 (Inhibitors present)	12 years	3 years	Tongue bite	July 2025	4-6	0	No Breakthrough bleeds noted
Pt-5 (Inhibitors present)	9 years	3 months	Facial bruise	July 2025	6-8	0	No Breakthrough bleeds noted
Pt-6 (Severe HA)	2 years	9 months	Buccal Mucosa	October 2025	26	0	No Breakthrough bleeds noted.

Table No. 1 Clinical profile of Hemophilia patients

DISCUSSION:

The WFH 2020 (World Federation of Hemophilia) guideline emphasizes that regular replacement (prophylaxis) with clotting factor concentrates or emicizumab is the standard of care for all patients with severe Hemophilia A to prevent bleeding and associated complications particularly musculoskeletal damage. The prophylactic therapy is to be initiated ideally before age of 3 years to alter the natural history of disease. Prophylaxis with clotting factor concentrate requires frequent hospital visits (2-3 times a week) and the need for intravenous access. 25-30% of patients develop inhibitors to factor VIII after several injections. This makes the use of emicizumab (given subcutaneously) more convenient and effective.

Bleeding Rate After Starting Emicizumab:

In the present study 6 patients with Moderate/Severe Hemophilia A were given emicizumab & the results were analyzed. Drug is procured through Government supply. Three patients received therapy for 22 months. 2 patients with severe Hemophilia A had zero bleeding as long as the therapy is continued and ABR of 4-6 during 5 months gap (due to shortage of supply) as compared to baseline ABR of 12-20 before starting emicizumab. One patient with moderate Hemophilia A (2% factor VIII levels) with frequent bleeds with arthropathy had zero bleeding rate even with 3 to 5 months gap of administration (both due to noncompliance & shortage of supply).

2 patients with inhibitors received emicizumab for 10 months with zero bleeding rate & complete resolution of joint swellings. One patient (2 years old-youngest in this group) received the drug for 6 months with zero bleeding after initiation of drug.

In the pooled analysis of HAVEN 1-4 trials there were rare breakthrough bleeds either spontaneous or traumatic while on prophylactic emicizumab therapy[3] .The mechanism of breakthrough bleeds despite adequate hemostatic level of emicizumab lies in the integrity of fibrin clot which forms after thrombin is generated in plasma by emicizumab. Fibrin clots formed in HA plasma have been demonstrated to be more fragile and weaker compared to normal fibrin clots and appear to be more susceptible to fibrinolysis.

The multicenter open label study by Shima et al. reported significant reduction in ABR in patients treated with emicizumab[1]. A retrospective cohort study by Oka et al. showed significant improvement in patients overall health and reduction in chronic pain after 1 year of emicizumab therapy. Nogami et al. and Zwer et al. extended these findings to larger cohorts and consistently demonstrated the efficacy of emicizumab in preventing overall & joint specific bleeding episodes in pediatric populations[1].

Safety:

No adverse drug reactions were noted in the present study. Shima et al. documented 133 adverse events , primarily minor with no reports of thrombotic events or thrombotic microangiopathy. Oka et al. reported adverse events in 42.1%, mainly local reactions. Nogami et al and Zwer et al also reported that injection site reactions were the most common adverse events[1].

Patient Satisfaction:

In this study all patients and their care givers expressed high satisfaction which is critical for adherence to the treatment and overall success. Patients and parents reported overall improvement in general health, less frequent / no visits to emergency department due to bleeds and reduction in school absenteeism. Oka et al & Kempton et al also reported high satisfaction scores.

Subcutaneous route of administration of emicizumab further adds to better adherence and patient satisfaction.

Dosage Of Emicizumab:
In the present study loading dose of 3mg/kg weekly for 4 weeks was given , maintenance dose of 3mg/kg once in 2 weeks or 6mg/kg once in 4 weeks was scheduled depending on feasibility and weight of patient to avoid wastage of drug (60 mg vials are supplied). Both are associated with zero bleeding rate.

The largest and longest study on emicizumab by Nita Radhakrishnan et al from India compared the efficacy of low dose vs standard dose of emicizumab[5]. Standard dose arm included loading dose of 3mg/kg once weekly 4 weeks followed by 3mg/kg once in 2weeks. Low dose schedule included 3mg/kg once in 4 weeks with or without loading dose. No difference was noted in the ABR & HJHS status with low dose & standard dose emicizumab during 12 months treatment. As both are equally effective, standard dose patients were also shifted to low dose[5].

A Study from India involving 10 patients on low dose emicizumab vs low dose factor VIII prophylaxis reported that all outcome measures are significantly better with low dose emicizumab[5]. Another work from India involving 8 patients with inhibitors reported bleed free status after 1 year with a dose as low as 0.8 to 2.6 mg/kg 4 weekly[5]. The use of doses as low as 0.8 to 1.6 mg/kg 4 weekly without loading dose has been reported by centers in other countries as well with favorable outcomes. Low doses are noted to maintain the factor VIII equivalent level of 1-3% as against 15% in the standard dose patients.

These reports support the use of low dose emicizumab which reduces the cost of treatment to < 50% especially in LMICs so that more number of patients can be given the benefit of prophylactic treatment.

Additional Clinical Applications :
Emicizumab has also shown efficacy in patients with acquired Hemophilia in whom factor VIIIa function is impaired by the presence of autoantibodies. Invitro studies have shown that even small amounts of Factor IXa are enough to guarantee hemostasis making emicizumab a potential option for patients with Hemophilia B. Refer Figure No. 1.

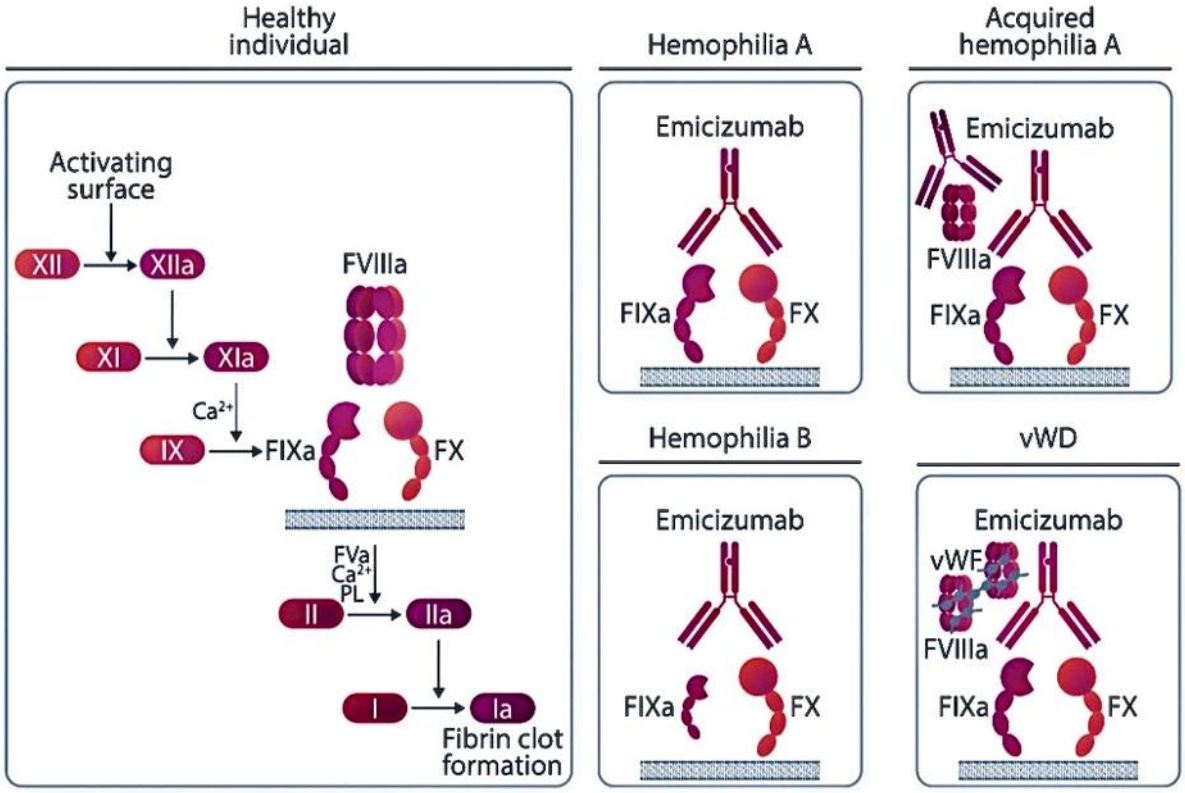

Figure No. 1. Procoagulant properties of emicizumab. Activated factor VIII (FVIIIa), activated factor IX (FIXa), Factor X (FX), activated factor V (FVa) and factor II (FII also known as prothrombin)[3].

In patients with Vonwillibrand disease especially in type 3 where the levels of both vonwillibrand factor and factor VIII are markedly reduced, emicizumab may be useful in maintaining hemostasis.

Government Supply of Emicizumab:
As emicizumab is expensive drug majority of hemophiliac patients coming to Government hospitals cannot procure it and depend on Government supply. Improving access to emicizumab requires enhanced State health budget. Hence systematic

efforts by the State & Central Governments are required for uninterrupted supply of this costly drug which improves the quality of life of children with Hemophilia A.

CONCLUSION:

Emicizumab is found to be game changer in the management of severe Hemophilia A with or without inhibitors. It helped in reversing the preexisting joint morbidity.

The relatively high cost and non availability of bypassing agents (like rFVIIa & aPCC) makes emicizumab especially useful in those with inhibitors. Subcutaneous route of emicizumab also overcomes the difficulty in finding repeated intravenous access for factor VIII replacement therapy especially in young children. Trials with lower maintenance dose (1.5mg/kg once in 2 wks or 3mg/kg once in 4 wks) offers access of emicizumab treatment for at least 50% more patients especially in LMICs (lower & middle-income countries).

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