Outcome of Emicizumab prophylaxis in twins with severe hemophilia A and inhibitors.

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Abstract

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Abstract

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Key clinical message

In our short period of experience, the molecule is found to be very safe and effective with almost zero spontaneous bleeds and no adverse events. The compliance is good with the subcutaneous route of administration especially in children with difficult venous access and high titer inhibitors.The treatment is cost-effective.

MeSH: Hemophilia A, Twins, Emicizumab, Bispecific / therapeutic use, Treatment Outcome

Outcome of Emicizumab prophylaxis in twins with severe hemophilia A and inhibitors

Development of Inhibitors against exogenous clotting factor concentrates is one of the most serious complications affecting ~30% of patients with severe hemophilia A[1]. Number of non-modifiable genetic factors and potentially modifiable environmental factors influence the risk of inhibitor formation [2]. About 40% risk of inhibitor formation is thought to be due to specific gene defects like intron 22 inversion [3]. The presence of inhibitors is associated with frequent bleeds, higher disease burden and treatment cost. The quality of life will be affected due to reduced physical activities and high mortality rare [4]. Emicizumab, a novel FVIII mimetic bispecific monoclonal antibody bridges FIXa and FX to facilitate effective haemostasis. It is indicated for routine prophylaxis to prevent bleeding or reduce the

frequency of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors [5]. We describe here the initial results of Emicizumab prophylaxis in twins diagnosed with severe Haemophilia A with inhibitors.

3 year 3 months old male child, one of the twins (Twin A), a known case of severe Hemophilia A with high titre inhibitors had presented in November 2020 with prolonged and profuse mucosal bleeding of 10 days duration at 2 years of age following lip injury. Bleeding was refractory to FEIBA (aPCC) administered for 6 days and a total of 12 doses. The diagnosis of Hemophilia A was made in early neonatal period, when his twin brother (Twin B) experienced prolonged bleeding from umbilical stump, which lead to further investigations. Twins were initiated on factor VIII replacement as an on -demand treatment from September 2019. The screening for inhibitors done as per WFH guidelines revealed high titer following 16 exposure days in the twin B and 20 exposure days in the twin A. Genetic study showed intron 22 inversions and the mother was detected to be a carrier.

Mucosal bleeding resolved with r FVII a therapy . Haemostasis could be achieved with 270 mcg/kg as single shot. The initial dose had to be followed by 90 mcg/kg /dose 2 doses 6 hourly and thereafter 12 hourly for 3 days as there was persistent oozing . Further evaluation revealed severe anaemia, Haemoglobin level of 5 gm/dl and a ferritin level of 12 ng/ml, requiring transfusion with packed red cells. He also had extensive thrombophlebitis (Figure -1).Considering the factors like severe bleeding phenotype with high-risk mutation, high ABR, presence of high titre inhibitor and difficult venous access, Emicizumab prophylaxis was started in December 2020. As of February 2022 twin A has completed 15 months of therapy. No spontaneous bleeding episodes (Zero bleeds) were observed. No Adverse events were observed except a traumatic muscle hematoma in Twin A on thigh following jump from height in Ultra sound revealed a mild hemarthrosis of knee. The event resolved in 2 days , after treatment with Tranexamic acid for 1 day. Emicizumab dosage schedule was continued unchanged and the event is considered as unrelated to treatment.

Encouraged by these positive results, the second child (twin B) who had been limping due to hemarthrosis of left ankle following 2 episodes of ankle bleeds was also initiated on Emicizumab in the month of June 2021. He completed 9 months of therapy and did not experience any bleeds, adverse events and his gait became normal.

(Baseline characteristics and response to emicizumab treatment are described in Table 1.)

Individuals with high titer inhibitors are treated with bypassing agents. Immune tolerance induction therapy is successful only in 70%-80% of patients with severe hemophilia A [6]. Twins had frequent bleeding phenotype, difficult venous access and extensive thrombophlebitis. Hence, the on-demand treatment was preferred even though primary prophylaxis is accepted as the only way to change the natural history of bleeding. However subsequent to development of refractoriness to FEIBA therapy, considering very high cost of rFVIIa, Covid -19 pandemic and travel restrictions, Emicizumab prophylaxis was initiated in Twin A. According to WFH guidelines, Emicizumab which is administered subcutaneously is considered more effective in bleed prevention and simpler to administer for patients with hemophilia A and persistent inhibitors who fail immune tolerance induction (ITI) or never underwent ITI [7].

Emicizumab has no structural relationship or sequence homology to FVIII and, as such, does not induce or enhance the development of direct inhibitors to FVIII and FVIII inhibitors do not bind to or neutralise emicizumab, therefore have no impact on its haemostatic activity [5]. The efficacy and safety of emicizumab has been demonstrated in one of the largest pivotal clinical trial programs in hemophilia A for patients with or without FVIII inhibitors [8]. Low bleed rates were maintained with long-term emicizumab prophylaxis, bleeding into target joints decreased substantially and no new ones formed. Compared with other available treatments the unique 4-week half-life offers consistent and sustained therapeutic drug levels with flexible dosing options, hence the maintenance dose can be selected based on physician and patient/caregiver dosing regimen preference. Because of the subcutaneous route of administration, frequent visits to a healthcare facility can be avoided [5].

By February 2022 Twin A and Twin B completed 15 and 9 months of therapy respectively .The average bleed frequency reduced from 10 and 12 bleeds per year to Zero bleeds after initiation of emicizumab prophylaxis and there were no adverse events. The results are similar to the outcomes described in HAVEN 1-4 clinical trials and in studies evaluating real world effectiveness of Emicizumab [9,10].

In general, Emicizumab prophylaxis is deemed tolerable, very few cases of thrombotic microangiopathy and thrombotic events were reported in patients receiving emicizumab prophylaxis when on average a cumulative amount of > 100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) for 24 hours or more were administered. Hence administration of aPCCs should be discontinued at least 24 hours prior to initiation of emicizumab. Emicizumab affects intrinsic pathway clotting-based laboratory tests, therefore, these test results should not be used to monitor emicizumab activity, determine dosing for factor replacement or anti-coagulation, or measure FVIII inhibitor titer. Chromogenic FVIII activity tests containing bovine proteins can be used to measure endogenous or infused FVIII activity and the chromogenic Bethesda assay can be used to measure FVIII inhibitors [5]. In the pivotal studies, emicizumab clinical outcomes were achieved without the use of assays to inform treatment decisions or make dose adjustments.

Emicizumab prophylaxis is being provided under the Kerala state policy by National Health Mission making use of the Patient Support Program of Roche India. As we work in resource restricted setting we analysed drug acquisition costs and impact on the total budget. We compared the acquisition cost of Emicizumab (for 15 months in twin A and 9 months in twin B) with expenses for same period in immediate past, when twins were on alternate antihemophilia therapy (the drug acquisition costs for on-demand therapy with factor VIII, later with bypassing agents following development of inhibitors). Emicizumab prophylaxis has costed only almost 1/3rd of prior anti haemophilia treatment and there was a significant reduction in the bleed rate in twins (Annexure 1).

We believe our case report is the first clinical report involving homozygous twins having intron 22 inversion on Emicizumab prophylaxis. There are five more children with inhibitors getting prophylaxis for more than 9 months from our institution and their follow up demonstrates that Emicizumab

prophylaxis is a treatment option with better effectiveness and lower costs than on-demand therapy with bypassing agents. Additionally, as twins had extensive thrombophlebitis and difficult venous access. Emicizumab treatment resulted in improved quality of life and convenience for the patient and his parents.

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Author's contributions

Dr. T. A. Sheela: Conception of the work. Analyzed the data and drafted the work.

Dr. U.S Jishell: Critical analysis of the case report.

Dr. Neethu. T. V: Helped in drafting the manuscript.

All authors have contributed equally to writing, review of manuscript and approve for submission.

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Table 1: Baseline characteristics and response to treatment.

Clinical characteristics	**Twin A**	**Twin B**
Significant past medical history	Spontaneous ecchymosis since 4 months. Prolonged bleeding following a minor injury on his finger at 6 months & Hemarthrosis of left knee at 10 months. Frequent hospitalization with mucosal and joint bleeds	Bleeding from umbilical stump. Frequent hospitalization with multiple ecchymosis and joint bleeds.
Annual bleed rate	8	10
Genetic diagnosis	Intron 22 inversions in both children and the mother was detected to be a carrier	
Age of onset of Inhibitors /Titre	1 yr 11 mo / 20.8 BU	1 y 10m / 8 BU
Exposure days (ED) before inhibitor development	20	16
Titre of inhibitor before starting Emicizumab	128 BU	40 BU
Duration of treatment	15 months	9 months
Bleeds during same period prior to treatment	10	12
Number of bleeds following Emicizumab	0	0

Figure 1;

Figure 1 – † .Twin B - Extensive thrombophlebitis with hemarthrosis left elbow.

Annexure -1. Cost comparison