Role of Emicizumab Therapy in treatment of Children with Hemophilia A Inhibitor

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ABSTRACT

Background: Hemophilia A is a hereditary condition that results in a lack of coagulation factor VIII. Emicizumab (ACE910) is a recombinant, humanized, bispecific monoclonal antibody that has been developed as a potential alternative treatment for hemophilia A in patients with inhibitors. **Aim:** To assess efficacy, safety of Emicizumab in treatment of children with hemophilia A of factor VIII inhibitors. **Patients and methods:** This prospective study was conducted on twenty patients with hemophilia A Inhibitors, admitted to pediatric department of El Helal insurance hospital, Sohag between 1st September 2023, 28 th February 2024. **Results:** 45% of patients had a history of serious conditions before starting treatment. Common problems due to the disease included knee joint pain (60%) and elbow joint pain (30%). Positive antibodies to Factor VIII were found in 40% of cases The mean age of starting Emicizumab was ±3.21 years. 70% received Emicizumab due to high antibody titre to factor VIII, 30% due to uncontrolled bleeding, 25% due to no response to factor VIII and 5% received Emicizumab without receiving Factor VIII. 65% of patient had no side effects, 35% had mild skin rash after treatment. 20% experienced serious conditions, including accidents and adenoidectomy operations. Patients visits decreased from three to two visits per month after emicizumab treatment. **Conclusion:** Emicizumab, a safe, effective treatment hemophilia, has no side effects, but common symptoms include mild bruises and a history of serious conditions.

Key words: Emicizumab, Hemophilia A inhibitors, Children.

INTRODUCTION

Hemophilia A is a hereditary condition caused by a lack of coagulation factor VIII; a protein essential for blood clotting. Individuals with this illness are at risk of spontaneous or traumatic bleeding, which can cause joint injury, chronic pain, disability if not properly addressed.[1]

Intravenous infusions of factor VIII were currently mainstay of care for people with severe types of haemophilia A. They are provided two to three times per week. Thirty percent of individuals who are exposed to factor VIII concentrates acquire neutralizing alloantibodies, commonly known as inhibitors.[2]

Inhibitors were a significant consequence of hemophilia A treatment because they make replacement factor VIII ineffective. This causes significant medical consequences, increased bleeding episodes, a higher risk of joint damage, as well as a lower health-related quality of life.[3]

Treatments for patients with a high titer of inhibitors (≥5 Bethesda units per milliliter) include eradication with induction of immune tolerance and episodic or prophylactic treatment with bypassing agents (recombinant activated factor VII [factor VIIa] or activated prothrombin complex concentrate). However, the efficacy of these bypassing agents is suboptimal, and both options involve frequent intravenous infusions that depend on adequate venous access. This can be a significant burden for patients, particularly those who have difficulty with venous access or who require long-term treatment.[4]

Emicizumab (ACE910) is a recombinant, humanized, bispecific monoclonal antibody that has been developed as a potential alternative treatment for hemophilia A in patients with inhibitors. It works by "bridging" activated factor IX and factor X, which restores the function of missing activated factor VIII, the deficiency of which is responsible for the bleeding phenotype in hemophilia A.[5]

Unlike traditional factor VIII replacement therapies, emicizumab does not rely on the presence of functional factor VIII, making it an attractive option for patients with inhibitors. In addition, emicizumab has a unique structure that is not expected to be affected by existing factor VIII inhibitors or to induce new development of such inhibitors.[6]

Emicizumab is administrated through subcutaneous injections, reducing the need for frequent intravenous infusions, this is a significant benefit over traditional factor VIII replacement therapies, which rely on regular intravenous infusions. Clinical trials have shown that emicizumab is able to effectively control bleeding in patients with hemophilia A and inhibitors. For example, a phase III clinical trial found that emicizumab was able to reduce the annualized bleeding rate by 96% compared to standard treatment with bypassing agents.[7]

It's important to notice, however, that emicizumab is not a curative treatment for hemophilia A, it's only able to control the bleeding episodes. Additionally, it's still a new and expensive treatment, whose long-term safety and efficacy have not been fully established. The treatment of hemophilia A in patients with inhibitors is a complex and challenging problem that requires ongoing research and the development of new therapies. Emicizumab represents an important step forward in the management of this condition and offers hope for patients and their families.[8]

We aimed to assess efficacy, safety of emicizumab in treatment of children with haemophilia A inhibitors.

Ethical Consideration

Information gathered from participants was strictly secret. No study participants were identifiable by name in any report or publication about this study. Before being admitted to this study, participants were informed about study's objective, nature, as well as risk-benefit evaluation. Informed consent was obtained.

Sample size

Sample size calculated based on the pilot study showing average of 21 pediatric Patients with hemophilia A inhibitor, admitted to pediatric department of El Helal insurance hospital With the allowable error of five percent (5%) and response distribution of 50%, a sample size for this study over the study period of 6 months will be 20 (Raosoft sample size calculator).[9]

Inclusion criteria: Congenital haemophilia A children aged three to fifteen years. Patients with a high factor VIII inhibitor titer (≥ five Bethesda units per millilitre) were undergoing treatment with bypassing drugs, either episodically or prophylactically.

Exclusion criteria: Children with congenital hemophilia A and their ages less than 3 years or more than 15. Patient responding to factor V111, other medical conditions that could affect study results or treatment safety, patients with other causes of bleeding, previous treatment with emicizumab, known allergy or sensitivity to emicizumab or its components and participation in other clinical studies.

Study methods:

This prospective study was conducted on twenty patients with hemophilia A Inhibitors, admitted to pediatric department of El Helal insurance hospital between 1st September 2023, 28 th February 2024.

All children included in the study were subjected to the following:

I- Full and careful history taking was obtained from patients and their parents Including: name, age, sex, address, order of birth, family history of hemophilia A, age at diagnosis and questions related to the disease manifestations and complications, presence and type of bleeding, history of blood transfusion, surgical procedure and hospital admission.

II - Clinical examination which includes: general examination and systemic examination.

111- laboratory evaluations: including

A. **Routine laboratory investigations:** Complete Blood Count (CBC), Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP), Liver and Kidney Function Tests, PT (Prothrombin Time), PTT (Partial Thromboplastin Time), INR (International Normalized Ratio).
B. **B. Specific laboratory investigations: Factor VIII levels, and Inhibitor Titre (Nijmegen-Bethesda Assay, NBA).** These tests assess overall health, inflammation, organ function, blood clotting, and specific factors related to conditions like hemophilia.

Bethesda Assay: Principle: This test found neutralizing antibodies (inhibitors) against FVIII: C.2. Nijmegen-modified Bethesda assay (NBA) was considered gold standard.[10] cases plasma, or serial dilutions of it, was combined with FVIII-containing standard human plasma (SHP), incubated at thirty-seven for two hours. incubation period was critical since FVIII:C inhibitors were temperature, time sensitive. Following incubation, FVIII:C residual activity (RA) was calculated, compared to a control mixture of SHP, inhibitor-free FVIII-deficient plasma.[11] Bethesda unit (BU) was defined as inhibitor concentration that neutralized fifty percent of FVIII:C in SHP. To assess inhibitor strength, a window of twenty-five to seventy five percent RA was advised. Outside of this window, samples were diluted, dilution with a RA closest to fifty percent (within range of twenty-five to seventy five percent) was used to calculate inhibitor strength.[12]

- After assessment of FVIII inhibitor, all patients with high level of inhibitors (≥5 Bethesda units per milliliter) received emicizumab according to the following schedule:

Usual Pediatric Dose for Hemophilia A with Inhibitors Newborn or Older: loading dose was three mg/kg subcutaneously once a week for 1st four weeks.

Maintenance dose: 1.5 mg/kg subcutaneously once a week, three mg/kg subcutaneously once every two weeks, six mg/kg subcutaneously once every four weeks.[11] Comments: Prophylactic use of bypassing agents should be discontinued day before commencing this medicine, prophylactic use of factor VIII (FVIII) products may be continued throughout 1st week of prophylaxis. Maintenance doses should be chosen depending on clinician discretion, cases adherence. Routine prophylaxis with factor VIII inhibitors was used to prevent or minimise frequency of bleeding episodes in newborns, older paediatric cases with haemophilia A (congenital factor VIII deficiency).[13]

Procedure

All individuals who got emicizumab received same dose on same schedule, were treated episodically with bypassing agents for breakthrough bleeding as needed. After at least twenty-four weeks of emicizumab prophylaxis, participants were instructed to continue taking maintenance therapy at 1.5 mg per kilogramme weekly or, if they had at least two spontaneous, clinically significant treated bleeding events in previous twenty-four weeks of emicizumab administration, both occurring after end of loading-dose period (termed "suboptimal control of bleeding"), to begin taking an increased dose of 3.0 mg per kilogramme weekly. criteria for bleeding events were adopted from scientific, standardisation committee of International Society on Thrombosis, Haemostasis. A bleeding incident was considered treated if it was immediately followed by administration of a haemophilia medicine that was reported to be effective for bleeding. Information on bleeding, drugs was recorded at time of a bleeding occurrence or medication administration, or at least once every eight days. Every four weeks, health-related quality of life was assessed, health status was assessed when a bleeding event occurs, every four weeks thereafter.

- **Lastly:** We follow up the patients who received emicizumab clinically and, in the laboratory, to assess their response to treatment, evaluated any reaction to treatment, and followed the frequency of bleeding for one month, three months, and six months after receiving treatment.

Statistical analysis:

The collected data were analyzed using SPSS v26 (IBM Inc., Chicago, IL, USA). Shapiro Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD). Quantitative non-parametric data were presented as median and interquartile range (IQR). Qualitative variables were presented as frequency and percentage (%).

RESULTS

Table (1): Demographic data of studied twenty patients with Hemophilia A Inhibitor.

		Number (N), Percent %
Sex	Male	19 (95%)
	Female	1 (5%)
Age (Years) ±SD		7.1 ± 3.01
Positive Parental Consanguinity		15 (75%)
Residence	Rural	18 (90%)
	Urban	2 (10%)

Table (1) showed, majority of patients were males (95%), while one patient was female (5%). Mean age of cases was 7.1 years, with Standard Deviation (SD ±3.01) years. Parental Consanguinity was reported in 75% of patients, and the majority of participants came from rural areas (90%).

Table (2): Main presenting symptoms of studied patients with Hemophilia A Inhibitor.

	Number (N), Percent %
Bruises	11 (55%)
External Bleeding	7 (35%)
Internal Bleeding	1 (5%)
Intracranial Hemorrhage (ICH)	1 (5%)
Site of bruises	
Limbs	3 (15%)
Trunk	1 (5%)
All over the body	3 (15%)
Gums	2 (10%)
Umbilicus	1 (5%)
Procedures	
After Circumcision	4 (20%)
After dental Procedures	1 (5%)
After canula	3 (15%)
After injections	1 (5%)
From scratch	1 (5%)

Table (2) showed that, bruises were the most prevalent symptom, reported by 55% of the participants. Intracranial hemorrhage (ICH) was observed in 5% of cases, while external bleeding and internal bleeding were reported in 35% and 5% of individuals, respectively. The distribution of symptoms across different anatomical sites is presented, with 5% occurring in the Trunk, 15% in the limbs, 15% throughout the entire body, 10% originating from the gum, and 5% from the umbilicus. Additionally, the conditions associated with these symptoms are outlined, with 15% occurring after canula procedures, 20% after circumcision, 5% after dental Procedures, 5% after injections, and 5% resulting from scratches.

Table (3): Distribution of patients according to severity of factor VIII deficiency.

	Value (N = 20)
Mild	1 (5%)
Mild to Moderate	4 (20%)
Moderate	8 (40%)
Severe	7 (35%)

Table (3) showed, mild hemophilia (> five percent to <40% factor ((F)VIII) activity), moderate hemophilia (one percent to five percent factor ((F)VIII) activity) and severe hemophilia (<1% factor ((F)VIII) activity). The data show that 5% had a mild form of the disease, 20% had mild to moderate, 40% had moderate, and 35% had severe disease.

Table (4): Diseases problems of studied patients.

	Value (N = 20)
Frequency of hospital admission	
Monthly	2 ± 0
Before management (times/Week)	3.1 ± 1.21
History of serious bleeding before start treatment	9 (45%)
Number of serious bleeding before start treatment	0.9 ± 1.8
Problems due to disease	
Knee joint pain	12 (60%)
Elbow joint pain	6 (30%)

Table (4) On average, participants went to the hospital twice per month. Before treatment initiation, they visited the hospital 3.1 times per week. Furthermore, 45% had a history of serious conditions before starting treatment, with an average of 0.9 serious conditions. Common problems due to the disease included knee joint pain (60%) and elbow joint pain (30%).

Table (5): Cause of receiving Emicizumab administration in the studied patients.

Emicizumab data	
Age of starting Emicizumab (Years)	4.86 ± 3.21
Cause of receiving Emicizumab	
Frequency of bleeding	
Bleeding from scrotum & gums	1 (5%)
Bleeding in urine	1 (5%)
Bleeding inside the eye	1 (5%)
Difficult canulation to receiving factor VIII	3 (15%)
Related to Factor VIII	**14 (70%)**
Not responding to factor VIII	5 (25%)
Positive antibody to factor VIII	8 (40%)
Start with it before staring factor VIII	1 (5%)

Table (5) The mean age of starting Emicizumab was 4.86 years, with a standard deviation of ±3.21 years. The reasons for receiving Emicizumab varied, with 70% related to Factor VIII, 25% not responding to Factor VIII, and 5% starting with Emicizumab without receiving Factor VIII. Positive antibodies to Factor VIII were found in 40% of cases.

Table (6): Follow up evaluation of studied patients.

	Value (N = 20)
Side effect of Emicizumzab	
No Reaction	13 (65%)
Mild skin rash	7 (35%)
Symptoms after receive treatment	
Mild bruises	13 (65%)
Mild to moderate bruises	4 (20%)
Moderate bruises	3 (15%)
History of serious condition after treatment	4 (20%)
Cause of serious condition	
Accident	2 (10%)
Operation adenoidectomy	2 (10%)

Table (6) showed that, of the participants, 65% reported no side effects of Emicizumab, while 35% experienced mild skin rash. Common symptoms after receiving treatment included mild bruises (65%), mild to moderate bruises (20%), and moderate bruises (15%). Additionally, 20% reported a history of serious conditions after treatment, with causes including accidents (10%) and adenoidectomy operations (10%).

Table (7): Comparison of manifestations before and after Emicizumab treatment in the studied patients.

	Before Emicizumab treatment	**After Emicizumab treatment**
Bruises	Always appear with minimal trauma	Rarely appear except with severe trauma
Bleeding	Mostly from orifices or tooth extraction	Rarely occurs
Blood transfusion	One transfusion per year	No need except for major operation
Hospital admission	Usually need hospital admission	Decrease the need for hospital admission

Table (7) showed good improvement of clinical manifestations as bruises and bleeding after Emicizumab treatment with decrease the need for blood transfusion and hospital admission.

DISCUSSION

Hemophilia A is a rare congenital bleeding illness characterized by a lack of coagulation factor VIII. Severe Hemophilia A, defined as plasma FVIII clotting activity <one percent of normal (FVIII: C < 1 IU/dl), can cause spontaneous bleeding, particularly in joints, resulting in painful hemophilic arthropathy, joint dysfunction. In affluent nations, mainstay of care for individuals with severe Hemophilia A was regular intravenous infusions of FVIII concentrates to prevent bleeding episodes (prophylactic therapy) .[14]

Our study found that bulk of individuals were men (ninety five percent), with only five percent woman. cases mean age was 7.1 years, with a standard variation of ±3.01 years. Symptoms began around nine years old, with a standard variation of ±3. Parental consanguinity was recorded in seventy five percent of cases, majority of participants lived in rural areas (ninty percent) rather than urban areas (ten percent). Our findings indicated that eighteen cases had a family history of a comparable illness. results show that fifty percent had a brother with a similar disease, ten percent had a sister, ten percent had a twin, five percent had a cousin, fifteen percent had an uncle with a comparable ailment.

Our findings were consistent with those of **Pipe et al.,[15]** who sought to assess efficacy, safety, pharmacokinetics of emicizumab prophylaxis administered every four weeks to persons with hemophilia A (HAVEN 4). cases aged twelve years, older with severe congenital haemophilia A (<one percent of normal FVIII activity in blood) or haemophilia A with FVIII inhibitors were recruited from three sites in Japan, Spain for

a run-in cohort, seventeen sites in Australia, Belgium, Japan, Poland, Spain, USA for a subsequent expansion cohort.

our findings showed that bruises were the most prevalent symptom, reported by 55% of the participants. Intracranial hemorrhage (ICH) was observed in 5% of cases, while external bleeding and internal bleeding were reported in 35% and 5% of individuals, respectively. The distribution of symptoms across different anatomical sites is presented, with 5% occurring in the back, 5% in the leg, 15% throughout the entire body, 10% originating from the gum, and 5% from the umbilicus. Additionally, the conditions associated with these symptoms are outlined, with 15% occurring after canula procedures, 20% after circumcision, 5% after teething, 5% after injections, and 5% resulting from scratches.

Den Uijl et al.[16] who reported that intracranial hemorrhage (IcH) was observed in 5% of cases, while external bleeding and internal bleeding were reported in 35% and 5% of individuals, respectively. majority of haemophilia cases have a known family history, so diagnosis can be made within hours of birth (or even prenatally if desired); for those who do not have a family history, severe form was typically diagnosed within 1st week of life lead to bruising/bleeding during birth, excess bleeding from circumcision, or excess bleeding from heel needle puncture.

Our investigation discovered that five percent had a weak type of condition, twenty percent had mild to moderate, forty percent had moderate, thirty five percent had severe. There were three types of haemophilia: mild (>five percent to < forty percent factor VIII activity), moderate (one percent to five percent factor VIII activity), severe (<one percent factor VIII activity).

Chalmers et al.[17] occurrence of ICH in newborns with haemophilia was well recognised, with an incidence of ~six percent by nine months of age for children with severe haemophilia A. After that, incidence flattens off dramatically, peaking at eight percent.

Our investigations showed that average, participants went to the hospital twice per month. Before treatment initiation, they visited the hospital 3.1 times per week. Furthermore, 45% had a history of serious conditions before starting treatment, with an average of 0.9 serious conditions. Common problems due to the disease included knee joint pain (60%) and elbow joint pain (30%).

In our study showed that mean age of starting Emicizumab was 4.86 years, with a standard deviation of ±3.21 years. reasons receiving Emicizumab varied, with 70% related to Factor VIII , 25% not responding to Factor VIII, and 5% starting with Emicizumab without receiving Factor VIII. Positive antibodies to Factor VIII were found in 40% of cases.

Le Quellec, S.[18] reported that HA children aged eight-eleven years, from baseline to week twenty-five following emicizumab prophylactic beginning.

Den Uijl et al.[16] reported that newborns with haemophilia did not exhibit joint or muscle bleeding until at least nine months of age, with median age of 1st joint bleed being 1.9 years old , an interquartile range of 1.2 to three years.

In our studies showed that, of the participants, 65% had no side effects of Emicizumab, while 35% experienced mild skin rash. Common symptoms after receiving treatment included mild bruises (65%), mild to moderate bruises (20%), and moderate bruises (15%). Additionally, 20% reported a history of serious conditions after treatment, e.g. after accidents (10%) and adenoidectomy operations (10%).

Pipe et al.[15] who established that safety assessment was a key component of research throughout development of new medications. Adverse events (AEs)

associated with emicizumab have been described in several clinical trial papers.

Conclusion

Regarding our results, we found that 65% reported no side effects of Emicizumab, while 35% experienced allergies. Common symptoms after receiving treatment included mild bruises (65%), mild to moderate bruises (20%), and moderate bruises (15%). Additionally, 20% reported a history of serious conditions after treatment, e.g. after accidents (10%) and adenoidectomy operations (10%). We can conclude that emicizumab is safe, and effective in hemophilia. Further studies with larger scales are needed with larger scales. Longer period is needed for follow up patients.

Young.[19] concluded that emicizumab is only effective in hemophilia A.

Recommendation:

Further studies with larger number of sample size to asses the efficacy of Emicizumab and any long term side effects.
Further studies with longer duration of follow up of Emicizumab injection site, clinical improvement and side effects.
Further studies to assess if Emicizumab can be used as first line treatment in hemophilia A.

Limitations:

Emicizumab is an expensive drug and only hemophilia A inhibitor indicating for receiving this treatment.
The study lacks the long duration of follow up of treatment to assess any long term side effects.

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