Section A-Research paper

Non-Factor Replacement Therapy: Emicizumab A Novel Therapy

Abdelrazek Elshiekh, Marwa Zakaria, Osama A. Gaber, Nada K Soliman, Laila M Sherief

Pediatric Department, Faculty of Medicine, Zagazig university

Email: nada.kamal.sol@gmail.com

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Abstract

Background: Emicizumab, a bispecific monoclonal antibody, was developed to meet the unfulfilled expectations of clotting factor replacement therapy. It has now established itself as the gold standard for the best preventive care for individuals with hemophilia A, both with and without inhibitors.

Keywords: Hemophilia, emicizumab, factor VIII

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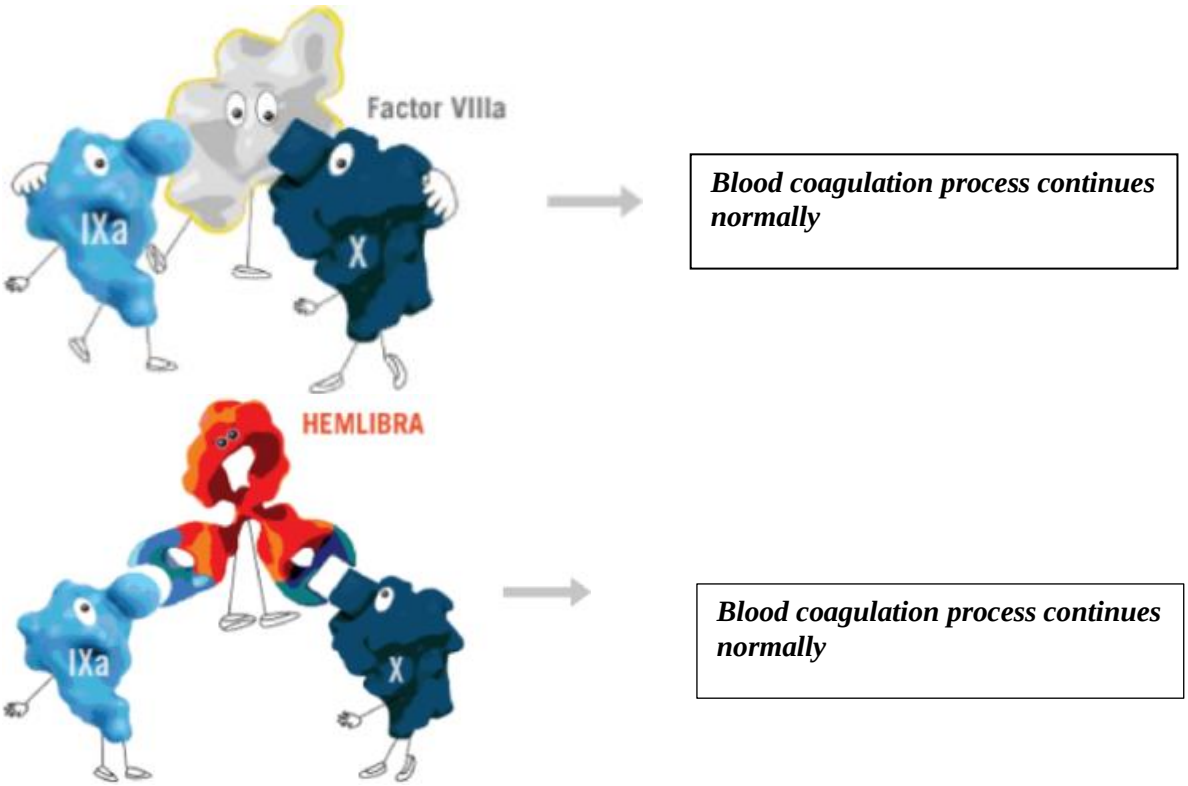
Introduction

Haemophilia A (HA) is an X-linked, recessive disorder due to a congenital lack of or decrease in plasma clotting factor VIII, which shows up as long-lasting, severe bleeding that occurs either spontaneously or following trauma.[1]. Hemophilia A patients may experience serious bleeding in their muscles and joints. The gradual and devastating co-morbidity known as hemophilic arthropathy is linked to hemophilia and is caused by repeated spontaneous joint bleeding. It is characterized by osteochondral degeneration and intra- and periarticular inflammation. Apart from inadequate levels of plasma clotting factor activity, recurrent bleeding episodes may be exacerbated by vascular instability resulting from neovascularization, vessel remodeling, and aberrant arterial leakiness. These factors collectively contribute to the progress of arthropathy. [2]. The main treatment for HA is replacement therapy, which can be regular infusions of FVIII concentrates to prevent bleeding episodes or administered on demand at the time of bleeding episodes exclusively. [3] neutralizing alloantibodies generated against infused FVIII (FVIII inhibitors) is a significant complication in the treatment of HA. In addition to other issues including the short half-life of FVIII concentrates, which necessitates frequent transfusions and challenging venous access,. [4]. Emicizumab, a long-half-life monoclonal antibody that bridges activated factor IX and factor X, replace the deficient activated factor VIII to effectively restore hemostasis. It is injected subcutaneously. Consequently, venous access and repeated infusions are not required. [5] Emicizumab is approved for use as regular prophylaxis in adult and pediatric hemophilia A patients, either with or without FVIII inhibitors, to prevent or decrease the frequency of bleeding episodes. [6]



Pharmacokinetics

❖**Absorption:**

After subcutaneous administration, the half-life of absorption is 1.61 days. The bioavailability varied from 80.4% to 93.1% after a 1 mg/kg subcutaneous injection. Similar pharmacokinetic patterns are observed in the abdomen, upper arm, and thigh after SC injection. When patients with hemophilia received emicizumab at a loading dose of 1 or 3 mg/kg Plasma concentrations reached a stable state after roughly 12 weeks. When emicizumab 3 mg/kg is administered once weekly for 4 weeks, mean trough plasma concentrations of 52.6 g/mL are attained in week 5.[7]

❖**Distribution**: The mean apparent volume of distribution is 10.4 L.

❖**Elimination:** The average apparent half life of elimination is estimated to be 26.9 +/- 9.1 days, whereas the average apparent clearance is found to be 0.27 L/day. Between 14.2 and 131 kg, the recorded clearance and volume of distribution of emicizumab showed a positive correlation with body weight. When emicizumab was administered according to body weight (mg/kg), exposure to the medication was similar for those with a range of body weights. There aren't many human studies looking into possible emicizumab drug-drug interactions.

Use in Specific Patient Population

❖**Hepatic and renal Impairment** A dose adjustment is not necessary for mild to moderate renal and hepatic impairment. But little research has been done on how emicizumab affects people who have severe liver and kidney failure**.** [8]

❖**Pregnancy Considerations**: Studies on emicizumab's effects on animal reproductive do not exist. There is insufficient data on emicizumab use in pregnant women to indicate a drug-related risk of congenital abnormalities and miscarriage. It is advised to administer emicizumab during pregnancy alone if the potential benefits for the mother are judged to outweigh any potential dangers to the fetus, according to the information contained in the product labeling. Women who are of reproductive age should use contraception while receiving emicizumab medication**.** [8]

❖**Breastfeeding Considerations:** The use of emicizumab with breastfeeding is not supported by clinical data. Since emicizumab is a large protein molecule with a high molecular weight, milk probably contains modest amounts of it. Emicizumab is unlikely to be absorbed since it is most likely removed by the infant's

digestive system. Clinicians should assess the benefits and risks of emicizumab exposure in breastfed infants, as well as the mother's need for emicizumab, in accordance with product labeling**.[**5]

Adverse Effects

The most common adverse medication responses associated with treatment are injection-site reactions. The four most often reported adverse medication responses are pyrexia (6%), diarrhea (6%), headache (15%), and arthralgia (15%). Additional negative effects include vertigo, lightheadedness, eye pain, and facial numbness. Rhabdomyolysis was an uncommon side effect that affected less than 1% of people receiving emicizumab.[9]

Thrombotic microangiopathy

Thrombotic microangiopathy (TMA) and other thrombotic issues have been observed in patients receiving emicizumab when activated prothrombin complex concentrate (aPCC) at a dosage exceeding 100 U/kg within a 24-hour period. The emicizumab key safety information states that 5.4% of patients who received at least one dosage of aPCC developed thrombotic events, whereas 8.1% of patients experienced TMA. TMA patients frequently suffer from acute renal injury, low platelet counts, and/or microangiopathic hemolytic anemia in the absence of a significant ADAMTS13 deficit. Thrombotic microangiopathy, cavernous sinus thrombosis, and thrombophlebitis were the other thrombotic events.[10]

When the benefit of aPCC outweighs the danger of producing a procoagulable state in an emergency, doctors should monitor patients for TMA and thromboembolism and terminate aPCC if symptoms develop. The use of both emicizumab and rFVIIa should theoretically raise the risk of thrombotic problems. Multiple pharmaceutical manufacturers have conducted an analysis of the data derived from the HAVEN trial. The study's findings indicate that the utilization of rFVIIa in conjunction with emicizumab prophylaxis did not result in any alterations to the safety profile of rFVIIa, as outlined in the product information. [11]

Monitoring

While determining plasma emicizumab levels is not required for treatment, there are several medical circumstances in which it may be helpful, such as confirming adherence. When circumstances call for breakthrough bleeding, antibody monitoring, or on-demand coagulation factors, monitoring is quite helpful. The enzyme-linked immunosorbent test (ELISA), which uses an anti-emicizumab antibody, is currently the only accurate detection method available. Currently, this assay cannot be used for commercial purposes; however, substitute assays may be employed. According to recent experiments and research, the test is highly exact and reproducible. [12]

FVIII activity assays can be used to track emicizumab levels since it resembles FVIII cofactor function, at least partially. Unfortunately, the standard 1-stage APTT-based assay is not helpful in this regard because the APTT is already normalized at subtherapeutic emicizumab doses (3-5 g/mL of emicizumab normalizes the aPTT, whereas therapeutic values are approximately 55 g/mL). [13] Two more activity tests could be used to get around this restriction. a modified aPTT technique that allows a linear relationship between emicizumab concentrations and clotting times by further diluting plasma samples. Using chromogenic FVIII activity tests using human FIXa and FX is an additional choice. Additionally, thrombin activation can be produced by a near-linear relationship between emicizumab concentrations and this assay, which leads to excessively low clotting durations**.** [14]

Emicizumab significantly impedes the results of many aPTT-based tests. The medication will also impact testing for protein C, S, and FVIII activity. Prothrombin time and fibrinogen-derived tests are slightly disrupted. Testing for lupus anticoagulant in patients receiving emicizumab presents challenges since it uses two different assays: aPTT-based and DRVVT-based, both of which have the potential to yield false-negative of false positive results respectively.[8]

Clinicians need to be mindful of assay interference when ordering FVIII activity or inhibitor titers for patients receiving emicizumab. Patients may be at risk of bleeding if clotting-based diagnostics overestimate FVIII activity. [15]

Emicizumab produces notable side effects and may produce undetectable anti-FVIII titers in patients with medically relevant inhibitors, according to the Bethesda tests. The administration of emicizumab can affect coagulation tests for up to six months after the previous dose, which is something that doctors should be

aware of because of its lengthy half-life. Lastly, regarding testing alternatives, physicians should confer with laboratory directors and request chromogenic tests that use a bovine reagent that is insensitive to emicizumab for FVIII activity and FVIII inhibitor testing. [16]

Emicizumab clinical trials

Numerous studies are being carried out to see if Emicizumab is effective for hemophiliac patients. Similar to the HOHOEMI, STASEY, and HAVEN trials [17]

The HAVEN trials used subcutaneous emicizumab injections at doses of 1.5 mg/kg once weekly, 3 mg/kg every two weeks, or 6 mg/kg every four weeks to assess the effectiveness of three different treatment plans. A total of four loading doses of 3 mg/kg were given weekly prior to the start of each treatment session. The HAVEN 1-4 trials showed that the weekly (QW), biweekly (Q2W), and quarterly (Q4W) treatment of emicizumab produced average annualized bleeding rates (ABR) of 1.6, 0.8, and 2.3, respectively [18].

At least 50% of patients (with a range of 56–90%) in each therapy cohort examined in the HAVEN trials did not have any episodes of treated bleeding. Over the course of all four studies, there was a steady increase in the percentage of people who had no bleeding incidents. Furthermore, it was noted that in patients taking part in the HAVEN 1-4 trials, emicizumab resulted in the resolution of 99% of target joints. Major joints including the hip, elbow, shoulder, wrist, knee, and ankle that experienced three or more bleeding episodes in a 24-week period were considered target joints [19] If there are two or more bleeding occurrences in a 52-week period in a joint that was previously designated as a target joint, it is considered resolved. [20]

Treatment regimens given to patients (Q2W) and (Q4W) in the HOHOEMI experiment, which involved Japanese pediatrics, showed (ABR) values of 1.3 and0.7, respectively. It is significant to remember that the trial's sample size was extremely small. [15]

HAVEN 1, 2 studies evaluated the effectiveness of emicizumab in hemophilia patients with with FVIII inhibitors only. The result of Emicizumab was ABRs of treated bleeds of 2.9, 0.3 respectively [21]

Patients without FVIII inhibitors were the only patients included in HAVEN 3 and HOHOEMI. Emicizumab was linked to treated bleeding ABRs of 1.5 and 1.3. [16] Patients with and without inhibitors were enrolled in the HAVEN 4 trial, and the ABR for treated bleeding was 2.4 (Q4W). [4]

STASEY experiment was done to assess emicizumab's effects on a cohort of 88 patients who had hemophilia with inhibitors. The trial found that the average (ABR) was 0.5. Seventeen of the eighty-eight patients in the cohort experienced bleeding episodes and were treated with rFVIIa. On the other hand, one patient got the typical FVIII care. There were no thromboembolic events or (TMA) incidents reported. [22]

Moreover, several Haven trials have demonstrated the effectiveness of emicizumab in lowering ABR and enhancing quality of life. For instance, the Haven 5 research looked at people with severe hemophilia A who were older than 12 and either had hemophilia A of any severity with inhibitors or severe hemophilia A without FVIII inhibitors.[23]Yang, Wang et al. and the Haven 6 trial examined the effects of emicizumab in individuals with moderate to mild hemophilia A who did not have inhibitors. [24]**.** A Haven 7 trial was conducted in infants (0–12 months old) with HA without inhibitors [25]

Over a five-year period, the MOTIVATE trial is a worldwide, prospective, observational study designed to assess the safety and effectiveness of ITI and/or emicizumab. About 120 hemophilia A patients with inhibitors will participate in the study, which will be carried out in a real-world clinical setting. The goals of the study include adverse drug responses, joint health, and bleeding outcomes, with a particular emphasis on thrombotic events. [26]

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