Utilization of Emicizumab in Acquired Factor VIII Deficiency

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: **Male, 91-year-old**
Final Diagnosis: **Acquired hemophilia A**
Symptoms: **Back pain • bleeding • hematuria**
Medication: **—**
Clinical Procedure: **—**
Specialty: **Hematology**

Objective: **Rare disease**
Background: Acquired hemophilia A (AHA) is a rare autoimmune disease caused by immunoglobulins that bind and inactive factor VIII, thereby predisposing to life-threatening bleeding. Bleeding is typically stabilized by utilizing bypassing agents, such as recombinant factor VIIa (rVIIa). Select case reports have demonstrated the success of alternative prophylaxis for clearance of factor VIII inhibitors through the use of emicizumab, a current FDA approved medication for treatment of congenital hemophilia A. In this case report we present the efficacy of utilizing emicizumab as a prophylactic agent in a patient that was unable to tolerate first-line therapy for prophylaxis.
Case Report: A 91-year-old male presented for ongoing hematuria for 5 weeks with prior workup unrevealing. He was given a day's course of recombinant factor VIIa to stabilize his bleeding and was started on cyclophosphamide and prednisone after a revealing hematological workup including activated partial thromboplastin time (aPTT) >100 seconds and factor VIII inhibitor level of 44 BU/mL. He continued to require VIIa infusions to control his bleeding and was started on emicizumab once stabilized. His bleeding remained controlled and his inhibitor decreased after 6 months of therapy with repeat factor VIII inhibitor level of 1.9 BU/mL.
Conclusions: The success of utilizing emicizumab for bleeding prophylaxis in AHA is demonstrated by this patient's resolution of bleeding. The high frequency of dosing and higher risk for thrombosis with factor VIIa, in conjunction with our patient's medical history and ease of administration, make emicizumab an ideal agent for bleeding prophylaxis while awaiting clearance of factor VIII inhibitors.

MeSH Keywords: **Complementary Therapies • Hematologic Agents • Hemophilia A**

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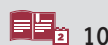
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Background

Acquired hemophilia A (AHA) is a rare autoimmune disease caused by immunoglobulin G antibodies that bind to specific domains on the factor VIII molecule, partially or completely neutralizing its coagulant function [1,2]. This reduced function can predispose a patient to life threatening bleeding, typically presenting as spontaneous bleeding with a prolonged PTT (partial thromboplastin time) without a personal or family history of coagulopathy. Approximately half of AHA cases are attributable to an underlying medical condition including autoimmune disease, malignancy, or drug/allergic reaction while the other half are idiopathic in nature [3]. The standard first-line treatment requires administration of bypassing agents, such as recombinant factor VIIa (rFVIIa) or active prothrombin complex citrate (aPCC), to stabilize bleeding [4–6]. However, adequate treatment of AHA remains a challenge due to delays in diagnosis, difficulty achieving hemostasis in the presence of factor VIII inhibitors, frequency of rFVIIa or activated prothrombin complex concentrate administration, and the immunosuppressive nature of the medications utilized for clearance of inhibitors causing complications, especially in elderly patients [7,8]. Recently, case reports have demonstrated the possibility of utilizing emicizumab, a monoclonal antibody that mimics factor VIII, as a potential prophylaxis therapy while awaiting inhibitor clearance given its less frequent infusion requirements, good hemostatic efficacy, and less overall side effects than the standard regimen [7,8]. In this patient case, we demonstrate the efficacy of utilizing emicizumab as a prophylactic agent in an elderly male with AHA.

Case Report

A 91-year-old Caucasian male with a past medical history of hypertension, benign prostatic hyperplasia, atrial fibrillation, and mitral valve replacement secondary to mitral stenosis presented to the Emergency Department (ED) with hematuria that was ongoing for 5 weeks. Prior to hospitalization, he had a cystoscopy that was not significant for any urological source of hematuria. Urology had been consulted and he was given a brief trial of continuous bladder irrigation and had a Foley catheter placed. Upon hematological workup, he was found to have a hemoglobin of 6.8 g/dL for which he received 1 unit of packed red blood cells, a platelet count of 193 000, aPTT (activated PTT) >100 seconds with a normal PT/INR (prothrombin time/international normalized ratio), a factor VIII level that was <1%, and a factor VIII inhibitor level of 44 BU/mL. Hematology/Oncology was consulted, and the patient was started on recombinant factor VIIa (NovoSeven) at a dose of 90 mcg/kg every 2 hours for a total duration of 24 hours. After receiving 12 doses, his bleeding stabilized, and he remained hemodynamically stable. To clear his factor VIII inhibitor, he was

started on prednisone 70 mg and cyclophosphamide 100 mg daily. One week later he reported worsening right lower abdominal pain with radiation to the back and the hip. He had a computed tomography (CT) scan of his abdomen/pelvis as well as his right hip, revealing a large intramuscular hematoma in his iliopsoas muscle secondary to continued bleeding, for which rheumatology was consulted but they found no evidence of connective tissue disease. He was also thrombocytopenic with a platelet count of 86 000. He was restarted on factor VIIa, but the frequency of infusion and recurrent bleed while off rFVIIa supplementation was a barrier to discharge. In this clinical setting, he was then started on emicizumab at a loading dose of 3 mg/kg subcutaneously weekly for 4 weeks then a maintenance dose of 1.5 mg/kg every 2 weeks. He was ultimately unable to continue with cyclophosphamide due to his persistent thrombocytopenia. He was monitored on prednisone alone via chromogenic factor VIII titers which were less than 55% until 6 months afterward where he had improvement to a factor VIII level of 86%. At this same time, his factor VIII inhibitor level was reassessed and was found to be 1.9 BU/mL. He continued to have excellent control of bleeding during this time, with no further episodes of hematuria, and was able to stop emicizumab prophylaxis. His repeat CT scan of his abdomen/pelvis was also repeated to assess his prior iliopsoas hematoma, which showed reduction in its size further supporting the control of bleeding. The prothrombotic effects of emicizumab were monitored objectively via physical examination, 2-dimensional echocardiography, and lower extremity duplexes on a monthly basis. He did not experience any side effects while receiving his emicizumab infusions and he recently had an additional factor VIII inhibitor titer ordered 3 weeks ago which is still pending.

Discussion

The utilization of emicizumab as a prophylactic agent for bleeding in acquired hemophilia A (AHA) has been detailed recently in a few case reports and is approved for treatment of congenital hemophilia A, but reports of its usage as a standard of care in AHA remain sparse. Al-Banaa et al. detailed a similar clinical scenario but in an 87-year-old female that had concerns of shortness of breath. On her workup, she had an identical hematological panel as in our case and had large chest wall and pelvic floor hematomas with no history of trauma or coagulopathy [8,9]. She was immediately treated with activated prothrombin complex concentrate and was transitioned to emicizumab on discharge with no recurrent bleeding in the 2-month follow-up period from her hospitalization [8]. In the present case, the patient had complete cessation of all spontaneous bleeding with normalization of his hemoglobin once started on emicizumab – identical to the outcome of the case in Al-Banaa et al. It has been postulated that the mechanism

of action of emicizumab is in its similarity to the structure and function of factor VIIIa [10]. Thus, we believe that it brings factor IXa and X close enough in proximity to allow factor IXa to catalyze factor X [10].

When assessing the application of utilizing emicizumab for prophylaxis while awaiting clearance of factor VIII inhibitors, it is important to consider the first-line therapy of bypassing agents for treatment. Duration of therapy is often judged subjectively, which proves to be challenging because of the shorter half-life and requirement for intravenous access [8]. Emicizumab is administered subcutaneously weekly initially and then biweekly, making it more ideal for management in the outpatient setting [8,9]. Thromboembolism remains a potential complication with treatment of bypassing agents as well, with rates as high as 2.9% of patients on rFVIIa and 4.8% of patients on aPCC in some studies [9]. Old age has also been found to be contributory to thromboembolic risk [8,9]. In this case, this would be problematic given our patient's history of atrial fibrillation, the presence of a mechanical mitral valve, and age. Although emicizumab has many advantages as a potential prophylactic agent, there have been 2 documented mortalities secondary to thrombotic microangiopathy [7–9]. However, this side effect has only been found in patients that were receiving both bypassing agents and emicizumab. This side effect has not been documented or studied in patients receiving emicizumab prophylaxis alone, which is why this case was able to be successfully managed with emicizumab.

Conclusions

The success of utilizing emicizumab as a therapy for prophylaxis of AHA was demonstrated by this patient's resolution of bleeding after failing the standard cyclophosphamide and prednisone regimen for factor VIII inhibitor clearance. The increased likelihood of thrombosis with the standard first-line therapy, in conjunction with our patient's past medical history, age, and the greater ease of administration in the outpatient setting made emicizumab an ideal agent for prophylaxis from a bleeding standpoint as factor VIII inhibitors are being cleared in AHA. Although shortcomings to therapy include documented mortality due to thrombotic microangiopathy, this has only been documented in patients who received bypassing treatment with emicizumab prophylaxis. These shortcomings can be minimized via objective monitoring with physical examination, echocardiography, and venous duplexes with subjective questioning.

Conflicts of interest

None.

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