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Case Report

Enhancing hemophilia A management: emicizumab as a cost-effective adjunct to standard therapy for inhibitor patients

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ABSTRACT

This case report discusses the cost-effectiveness of emicizumab + low dose recombinant factor VIIa (rFVIIa) therapy in management of mild hemophilia A with inhibitors. Initial treatment with recombinant factor VIII was complicated by inhibitor development, leading to recurrent bleeding and hematoma formation. After administering full dose rFVIIa to patient for controlling bleeding episodes initially, patient was transitioned to emicizumab alongside low-dose recombinant factor VIIa, which proved efficacious and cost-effective. This case highlights the potential of emicizumab to alleviate the financial burden on patients and healthcare systems, improving treatment access and outcomes for a broader hemophilia patient population.

Keywords: Hemophilia A, Emicizumab, Low dose recombinant factor VIIa, Inhibitors pharmacoeconomics

INTRODUCTION

Congenital hemophilia A is an inherited X-linked bleeding disorder, arising from the deficiency of coagulation factor VIII (FVIII), which exhibits a spectrum of clinical phenotypes. The hallmark of the disease lies in its propensity for recurrent bleeding, with joints being the most commonly affected sites.[1] If left untreated, this bleeding tendency can lead to hemophilic arthropathy.

Classification of hemophilia is based on the levels of coagulation FVIII: mild (FVIII between 6% and 40% of the normal value), moderate (FVIII between 1% and 5% of the normal value), and severe (FVIII less than 1% of the normal value).[1] Spontaneous bleeding occurrences are rare in mild hemophilia cases and typically result from trauma or surgical interventions. Functional limitations are uncommon in patients with mild hemophilia, who are primarily managed on-demand.

The development of inhibitors in hemophilia A involves polyclonal IgG antibodies, triggered by the presentation of novel or immunologically altered FVIII to the immune system. These inhibitors are categorized based on their kinetics and extent of inhibition. Type I inhibitors, prevalent in severe cases, follow second-order kinetics and completely inactivate FVIII, while type II inhibitors, observed in acquired or mild cases, exhibit complex kinetics and incompletely inhibit FVIII. Multiple risk factors, including genetic factors (such as the type of mutation and HLA class II polymorphism) and non-genetic factors (including immunological factors, surgical and traumatic events, treatment-related factors, and the modality of FVIII infusion), contribute to inhibitor development.[2]

CASE REPORT

A 63-year-old male, who volunteered to donate his kidney to his daughter, presented to the anesthetist for pre-

anesthetic consultation. His medical history revealed no significant comorbidities, and physical examination findings were unremarkable. However, during a detailed interview, the patient disclosed a history of prolonged bleeding following minor traumas since childhood, which he had never addressed medically due to the absence of significant bleeding episodes.

The suspicion of a bleeding disorder was heightened by a mildly elevated activated partial thromboplastin time (aPTT) of 46 seconds, beyond the normal range of 21-35 seconds. Further laboratory investigations confirmed low factor VIII levels at 16%, confirming a diagnosis of mild hemophilia A. Despite counselling regarding the surgical risks associated with his condition, the patient insisted on proceeding with the renal transplant surgery. Before the surgery, mixing studies were performed to assess inhibitor levels, yielding a negative result.

Following the successful surgery, on postoperative day 1, a significant hematoma measuring 6×4 cm formed around the surgical incision site. Additionally, a drop in hemoglobin levels from 13 g/dl to 7 g/dl (normal range: 12-16 g/dl) was noted. Despite evacuation of the hematoma and continued administration of recombinant factor VIII, the hematoma reformed the next day. Subsequent factor VIII inhibitor testing revealed a high titer of 24 Bethesda Units. Consequently, the patient was transitioned to recombinant factor VIIa (rFVIIa) infusion at a dose of 90 mcg/kg every 4 hours, leading to resolution of the hematoma.

The patient reported intermittent bleeding episodes in the ensuing months, necessitating repeated rFVIIa therapy, which proved to be financially burdensome. In a trial approach, the patient's treatment regimen was modified during a subsequent bleeding episode. He was initiated on emicizumab therapy at a dose of 1.5 mg/kg subcutaneously weekly, in addition to low-dose rFVIIa at 45 mcg/kg every 6 hours for 3 days, resulting in successful hemostasis. Subsequently, the patient was maintained on emicizumab at a dose of 3 mg/kg every 2 weeks, leading to sustained improvement and return to normalcy.

DISCUSSION

The development of neutralizing alloantibodies, or inhibitors, following therapeutic factor VIII (FVIII) infusions presents a formidable challenge in the management of hemophilia A. In mild cases, the cumulative incidence of inhibitors is estimated to be approximately 5–10%.[3] Recombinant factor VIIa (rFVIIa) was initially designed for the treatment of hemophilic patients with inhibitors, offering promising results.[4] rFVIIa has been initially approved at a dose of 90 mcg/kg every 2-3 hours until clinical evidence of good hemostasis is achieved. However, its short half-life (2-3 hours in adults) necessitates frequent infusions, typically every 2-6 hours, adding to treatment complexity and cost.[3]

In our patient's case, rFVIIa therapy at a dose of 90 mcg/kg every 4 hours for 3 days was initiated, which incurred substantial costs as detailed in Table 1. Recognizing the need for a more cost-effective yet efficacious treatment approach, the patient was transitioned to emicizumab, a recombinant, humanized, bispecific monoclonal antibody. Emicizumab functions by bridging factor IXa and factor X to restore the function of missing activated factor VIII, without being affected by existing inhibitors or inducing new inhibitor development.[5]

Table 1: Cost breakdown of normal dose rFVIIa therapy (body weight=65 kg).

Parameters	Cost breakdown
Cost of 1 mg rFVIIa -	531.40 USD
Cost of rFVIIa therapy for 1 day -	6 mg given 4 hourly=36 mg/day=Rs. 19130.43 USD
Total cost of rFVIIa therapy for 3 days -	57391.28 USD (19130.43×3)

The patient was successfully managed with a combination therapy of emicizumab at a dose of 1.5 mg/kg subcutaneously weekly, along with low-dose rFVIIa at 45 mcg/kg every 6 hours for 3 days, followed by emicizumab maintenance therapy at a dose of 3 mg/kg every 2 weeks. The cost analysis presented in Table 2 demonstrates a significant cost differential between the two treatment modalities, with the combined emicizumab and low-dose rFVIIa therapy proving to be substantially more cost-effective. It is to be noted that all costs incurred here are barred by the healthcare system.

Table 2: Cost breakdown of emicizumab + low dose rFVIIa therapy (body weight=65 kg).

Parameters	Cost breakdown
Cost of 1 mg rFVIIa	531.40 USD
Cost of low dose rFVIIa therapy for 1 day	3 mg given 6 hourly=12 mg/day=6376.81 USD
Total cost of rFVIIa therapy for 3 days	19130.43 USD (6376.81×3)
Cost of emicizumab 90 mg weekly	531.40 USD×2=1062.80 USD
Cost of emicizumab 180 mg 2 weekly	1062.80 USD
Net total cost	20193.23 USD (19130.43+1062.80)
Cost difference in both therapies	37198.05 USD (57391.28-20193.23)

This cost differential is of paramount importance, particularly in resource-limited settings such as India, where the prevalence of hemophilia is notable. Data from India in 2011 reported a significant burden of bleeding disorders, including hemophilia A, with inhibitor prevalence ranging from 8.2 to 13 percent.[6] Given that many patients belong to rural areas and face financial constraints, the adoption of cost-effective treatment

strategies like emicizumab-based therapy could alleviate the economic burden on both patients and healthcare systems. Success in implementing such strategies could potentially lead to significant cost savings and the ability to extend treatment access to a larger patient population, thereby addressing a critical unmet need in hemophilia care.

CONCLUSION

Emicizumab-based therapy demonstrated successful hemostasis and sustained improvement in managing hemophilia A with inhibitors. Compared to traditional recombinant factor VIII and recombinant factor VIIa treatments, emicizumab showed significant cost savings, making it a more economically viable option. The case highlights the potential of emicizumab to alleviate the financial burden on patients and healthcare systems, improving treatment access and outcomes for a broader hemophilia patient population.

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