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CASE REPORT

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Emicizumab in hemophilia A with inhibitors: clinical and economic impact of its use in a Cuban patient

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ABSTRACT

Introduction: The management of a patient with severe hemophilia A with inhibitors is a challenge for any health-care professional. The present analysis shows the clinical and economic impact of the therapeutic approach in the most critical patient of the Cuban Hemophilia Cohort.
Objective: To evaluate the economic and clinical impact of the implementation of Emicizumab therapy in the first Cuban patient.
Case presentation: Adult patient who started to use recombinant activated factor VII episodically during adolescence when he was diagnosed with the presence of high-responding antibodies against factor VIII. During the years that he used this medication, he had recorded between 95 and 105 bleeds annually. In 2018, he presented with severe hemoperitoneum and was admitted to the intensive care unit with high doses of recombinant factor VII activated, multiple transfusions of packed red blood cells, and other care typical of a critically ill patient; his evolution was satisfactory. He started emicizumab prophylaxis 7 months after this event and is currently on Week 133 of treatment. He has not presented with further bleeding, nor has he reported adverse reactions to this treatment. The biannual cost savings for on-demand treatment and prophylaxis have been US $792,509.24.
Conclusions: Emicizumab prophylaxis improved the patient's quality of life and that of his family. From the perspective of the Cuban health system, the use of emicizumab in this clinical case was satisfactory and its experience will be analyzed in new patients.

Keywords: Costs, Emicizumab, Hemophilia, Inhibitor, NovoSeven

Introduction

Hemophilia A is a congenital hemorrhagic coagulopathy characterized by the alteration of the gene encoding for factor VIII (FVIII), one of the cofactors involved in the coagulation mechanism that ensures adequate thrombin generation, formation of a resistant clot, and cessation of bleeding (1). One of the most important determinants of the severity of bleeding manifestations is the degree of FVIII deficiency; patients are classified as severe, moderate, and mild. The bleeds observed are usually diverse, but bleeds occurring in the musculoskeletal system are the most common and cause permanent disability if not treated opportunely (2).

Severe patients may experience two or three bleeding events in 1 week; primary prophylaxis, suggested to be started from the first years of life, is the indicated treatment for preventing serious consequences of the disease. Currently, this therapy is recommended with conventional intravenous replacement products or with emicizumab, a novel subcutaneous bispecific monoclonal antibody (Hemlibra®, F Hoffmann-La Roche, Basel, Switzerland) (3).

The presence of neutralizing alloantibodies is one of the disease-related complications that precludes classical replacement therapy and requires the use of bridging agents such as recombinant factor VII activated (rFVIIa, NovoSevenRT®, NovoNordisk, Bagvaerd, Denmark) or activated prothrombin complex concentrate (FEIBA, Factor Eight Inhibitor Bypass Activity; Takeda Pharmaceutical Company Limited, Lexington, MA, USA), in sporadic treatment schemes or as part of immune tolerance protocols to reduce those antibodies in a prolonged or permanent manner (4).

Since 2018, based on efficacy results in the HAVEN 1–4 clinical trials, emicizumab prophylaxis was approved for

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patients with hemophilia A with inhibitors (5-7). In the last edition of the disease management guidelines of the World Federation of Hemophilia, it was prescribed to be used for these cases (3).

The approximate costs (US) were emicizumab $87.14 per mg (period 2019–2020), rFVIIa $755.72 per mg (period 2017–2018), tranexamic acid $0.84 by tablets and $4.7 by ampoules, each packed red blood cell transfusion $300, and the intensive unit care hospitalization $11,500 for 12 days.

The work presented here aims to show the economic and clinical impact of treating the first Cuban patient with severe hemophilia A and high-responding inhibitors before and after starting therapy with emicizumab.

Case presentation

A 28-year-old male patient presented with severe hemophilia A with high-responding inhibitors (titers up to 16 BU/mL), family history of hemophilia, and diagnosis during the infant stage. In the first years of life, therapy with hemocomponents was used: cryoprecipitate and fresh frozen plasma, and the patient started to report urticaria and other anaphylaxis secondary to this treatment. For this reason, he was treated once with first-generation recombinant FVIII concentrate and also started to experience dyspnea, urticaria, and shortness of breath; the medication was withdrawn and treatment with steroids and antihistamines was implemented. Immunoglobulin A deficiency was suspected and supported by immunological studies.

Thereafter, the use of second- or third-generation recombinant FVIII concentrates was recommended, but those options were not available in his country. Shortly thereafter, he started with high inhibitor titers and treatment with rFVIIa was suggested, starting from 14 years of age and continuing until the start of the current therapy. Treatment was always sporadic; over the years the demand for this therapy increased and could not be administered as prophylaxis on a stable basis. He had multiple bleeding events, between 95 and 105 per year, in the knee, elbow, ankle, and interphalangeal joints, in addition to hematuria and muscle bleeds. The amounts of rFVIIa varied according to the intensity of the event; the usual dose for bleeding control was 120–150 µg/kg/dose every 2 or 3 hours.

Complications of the disease appeared, such as difficulty walking, prolonged wheelchair use, development of hypertension, and cardiac arrhythmias requiring treatment with two antihypertensive drugs, and venous accesses became increasingly difficult to obtain. Changes in ventilatory dynamics occurred due to atrophy of the muscles involved in respiratory function.

Seven months prior to starting treatment with emicizumab, the patient was admitted to the intensive care unit (ICU) with profuse spontaneous intra-abdominal bleeding accompanied by a decrease in hemoglobin levels from 14.0 to 7.0 g/dL, confirmed by physical examination and serial ultrasounds. Treatment was started with rFVIIa at doses of 120 µg/kg every 2 hours; after 48 hours, bleeding did not subside and doses of 180 µg/kg every 3 hours for 24 hours were used. At 96 hours, there was mild clinical improvement and dose de-escalation was restarted at 120 µg/kg every 3 hours and then every 6 hours until discontinuation 7 days after this treatment was started. During this admission, 350 mg (NovoSeven-RT vial, 1 mg) was used and the patient was transfused with 4 units of packed red blood cells. The patient was discharged 12 days after his hospital stay with sequelae of this serious bleeding.

In his technical training, working, and social environment, he had many limitations.

In March 2019, subcutaneous emicizumab treatment was started, a first month of loading at 3 mg/kg/weekly for 4 weeks and then at a dose of 1.5 mg/kg/weekly. After starting this treatment, he had no spontaneous or posttraumatic bleeding, no side effects to the drug, no hospitalizations or other concomitant therapies. Hypertension was controlled by a single antihypertensive and disturbances in respiratory dynamics disappeared.

A direct health care costs comparison was made, estimating the cost of the years 2017 and 2018 with the use of a bypass agent, and compared with the years 2019 and 2020 with the use of emicizumab. Indirect costs were not included. There were no hospitalizations in 2017, he presented multiple joint bleeds and 1,200 mg of rFVIIa was used. In 2018, the patient took 1,139 mg of rFVIIa: 789 mg for treatment of episodes of hemarthrosis and muscle hematomas and 350 mg during ICU admission (Tab. I). The biannual cost (2017 and 2018) of rFVIIa was US $1,780,691.96, and the treatment with emicizumab (2019 and 2020) was US $988,182.72 per year. The biannual savings of the prophylactic treatment with respect to episodic treatment were US $792,509.24. He did not present with joint bleedings, hospitalizations, or other hemorrhagic events (Tab. II).

TABLE I - Annual consumption of products or medical services

	Consumption			
Product/Service	**2017**	**2018**	**2019**	**2020**
rFVIIa (mg)	1200	1139	0	0
Emicizumab (mg)	0	0	5880	5460
Tranexamic acid (tablets)	360	0	0	0
Tranexamic acid (ampoules)	0	72	0	0
Transfusion (units)	0	4	0	0
Hospitalization (days)	0	12	0	0

rFVIIa, recombinant factor VII activated.

He currently works in a private family business. Initially he was walking 5 km/day, but now he walks 3 km/day because he has incorporated mechanical and aerobic exercises. The beginning of treatment achievements with emicizumab could be observed 2 months after starting treatment. Total treatment time is 133 weeks.

TABLE II - Comparison of direct costs by products and medical services

	Direct costs ($)			
Product/ Service	**2017**	**2018**	**2019**	**2020**
rFVIIa	906,864.00	860,765.08	–	–
Emicizumab	–	–	512,391.04	475,791.68
Tranexamic acid (tablets)	302.40	–	–	–
Tranexamic acid (ampoules)	–	60.48	–	–
Transfusion	–	1,200.00	–	–
Hospitalization	–	11,500.00	–	–
Annual costs ($)	907,166.40	873,525.56	512,391.04	475,791.68
Cost 2017-2018 ($)	1,780,691.96		Cost 2019-2020	988,182.72
Savings (Biannual comparison) $792,509.24				

rFVIIa, recombinant factor VII activated.

Discussion

Conventional therapies for the treatment of patients with hemophilia and inhibitors were developed more than 30 years ago and changed the lives of patients with these complications (8). These products are used in immune tolerance therapy schemes or very frequent episodic treatment, with the disadvantage that patients develop poor venous access over the medium and long term. rFVIIa is a product with demonstrated safety and efficacy, though the latter is less than that achievable with replacement therapy schemes in patients without inhibitors. One disadvantage is the high cost of the product and that some countries cannot access this therapy for that reason (9,10).

rFVIIa controlled bleeds at higher than standard doses (90–120 µg/kg) (10). In recent years, bleeds were very recurrent, required regular infusions, and venous accesses became increasingly unfavorable. It was imminent to try to include him in another treatment scheme in order to improve his quality of life.

Emicizumab is a recombinant humanized and bispecific monoclonal antibody that restores the function of activated FVIII in deficiency, achieving effective hemostasis in patients with hemophilia A. This antibody has a high bioavailability and a half-life of approximately 24 to 30 days (9,11). With the prophylactic use of this antibody, the patient was able to return to social life free from bleeding events and side effects, as seen in other reports (12).

This case presentation demonstrates that, despite the significant cost of the drug, there was a significant reduction in overall costs with emicizumab prophylaxis, in addition to the benefits on quality of life of the patient.

The Barthel Index (BI) is a tool to measure a person's ability to perform ten activities of daily living, considered basic, and the patient obtained a pre-emicizumab score of 37 points, which places him in a high dependency range (13). Recently, the test was repeated and a score of 100 points was obtained, meaning independence.

An analysis of patients with hemophilia A inhibitors treated on demand with rFVIIa and prothrombin complex concentrate demonstrated the need to search for more efficient alternatives to the established bridging therapies because they are very expensive, require regular infusions, and do not always achieve the required speed of control of bleeding events and pain (14). Zhou et al (15) published an economic study model to predict short- and long-term outcomes of both emicizumab and FVIII prophylaxis. This longitudinal predictive study demonstrated that the use of this monoclonal antibody is cost-effective, in addition to other benefits for the patient, family, and society.

The management of a hemophilic patient is a challenge for any healthcare professional, even more so when it comes to severe hemophilia A with inhibitors. Emicizumab, an innovative therapy that since 2019 was introduced in the treatment of the first patient in Cuba, established a regimen for the prophylaxis of the disease. The evolution has been very favorable in all aspects, with the resultant disuse of other therapies; he is now a patient who has moved on from a life full of limitations to one with a broad horizon of future projects and plans.

Data on a single patient should not be generalized; however, this case suggests that when the costs are taken into account, prophylaxis with emicizumab in patients with hemophilia A and inhibitors may be beneficial from both a clinical and economic perspective.

Conclusions

Emicizumab prophylaxis improved the patient's quality of life, regaining his mobility and allowing him to join his work, social and family life, improving his quality of life and that of his family.

In biannual comparison of direct costs of prophylaxis, emicizumab reduced costs of care associated with prophylaxis by US $792,509.24 compared to the use of rFVIIa in the prior period. Bleeding events decreased from 105 to zero, avoiding emergency care and hospitalizations. From the perspective of the Cuban health system, the use of emicizumab in this clinical case was satisfactory and its experience will be analyzed in new patients.

Authorship contribution

DCG: original idea, data collection, writing of the manuscript
IAS: data collection, manuscript review
CMA: original idea, manuscript review
AGMB: original idea, data management, manuscript review

Disclosures

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