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Case report

[Translated article] Utilization of emicizumab in the treatment of a case of acquired haemophilia A

Utilización de emicizumab en el tratamiento de un caso de hemofília A adquirida

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Introduction

Acquired haemophilia A (AHA), unlike haemophilia A (HA), is a bleeding disorder of autoimmune origin that occurs in both men and women. It is a rare, poorly understood, under-diagnosed disease with a high mortality rate.[1] It is caused when the body develops antibodies to factor VIII (FVIII inhibitor). In 52% of patients, the cause is unknown. In other patients, it has been associated with autoimmune disease, cancer, pregnancy, vaccines, and/or pharmacological treatment.[2] Manifestations range from intense bleeding (generally after trauma or childbirth) to spontaneous bleeding of varying location and severity. Diagnosis is difficult, not only because of a lack of knowledge, but also because it is often masked, as in patients receiving anticoagulation.[3] Rapid diagnosis is essential for early initiation of antihaemorrhagic therapy.[4]

The mainstays of treatment are haemostatic agents other than FVIII, to restore haemostasis, and immunosuppressive therapy, to eradicate inhibitors.[5] Haemostatic therapy in patients presenting with severe bleeding or the need for urgent surgery is based on bypass agents (activated prothrombin complex concentrate or rFVIIa) or alternatively, porcine recombinant FVIII, which carries lower thrombotic risk. Immunosuppressive therapy to eradicate inhibitors involves the use of corticosteroids in monotherapy or combined with cyclophosphamide and/or rituximab. Combination therapy is associated with a more rapid response, but carries a higher risk of complications.[5]

Emicizumab is a bispecific monoclonal antibody that mimics FVIII activity, but is not indicated in AHA; however, by extrapolation of its results in HA with inhibitors, it may be a valid option in this disease.

Case description

A 66-year-old male patient with a history of liver cirrhosis due to alcohol use disorder was admitted to the emergency department from primary care due to oedema in the legs and poor general condition. He was admitted to the gastrointestinal department with a diagnosis of severe peptic oesophagitis and giant hiatal hernia. During the first days of admission, an extensive spontaneous haematoma was observed on the posterior aspect of the left thigh, with oedema and discomfort on palpation. The patient had not previously presented with haemostatic abnormalities or anaemia. At 72 h, there was spontaneous improvement, but this was followed by a submandibular haematoma accompanied by odynophagia that evolved into mild bleeding in the mouth. Exploratory maxillofacial surgery revealed a subcutaneous haematoma in the submental areas and on the floor of the mouth, with no apparent collection, swelling, hardening, or signs of infection. At this point, the clinical team decided not to modify the treatment.

For 17 days, the patient presented with new spontaneous haematomas that increased in size in different locations (neck, thigh, arm, and side), in the absence of any trauma that would explain them. Laboratory tests showed anaemia with a haemoglobin level of 6.5 g/dL, so the patient was administered 10 doses of intravenous iron (200 mg/48 h) and 10 blood transfusions.

After evaluation by the haematology team, a diagnosis of AHA was made. As the patient had no history of oncologic, autoimmune, or other risk factors associated with AHA, a diagnosis of idiopathic AHA was made. Among the initial coagulation tests conducted during diagnosis, the following findings are notable: activated partial thromboplastin time 80 s, prothrombin time 13.2 s, and fibrinogen 292 mg/dL. Special coagulation tests found negative lupus anticoagulant, FVIII activity 9%, and Bethesda units 1.90.[1] Immunosuppressive treatment was initiated with intravenous methylprednisolone (90 mg/12 h on day 1 as a loading dose, continuing with 80 mg/d oral) and support with intravenous rFVIIa 5 mg/6 h as a bypass agent until attaining haemostatic stability (Fig. 1). The costal haematoma worsened and so 2 red cell concentrates were administered.

We decided to initiate treatment with the off-label use of emicizumab. After obtaining the patient's informed consent, subcutaneous emicizumab 210 mg (3 mg/kg) was administered.[6] Treatment with rFVIIa was maintained for 3 days every 6 h followed by another 3 days every 12 h. FVIII activity was determined using bovine chromogenic assay given that bovine coagulation factors are not sensitive to emicizumab.[7]

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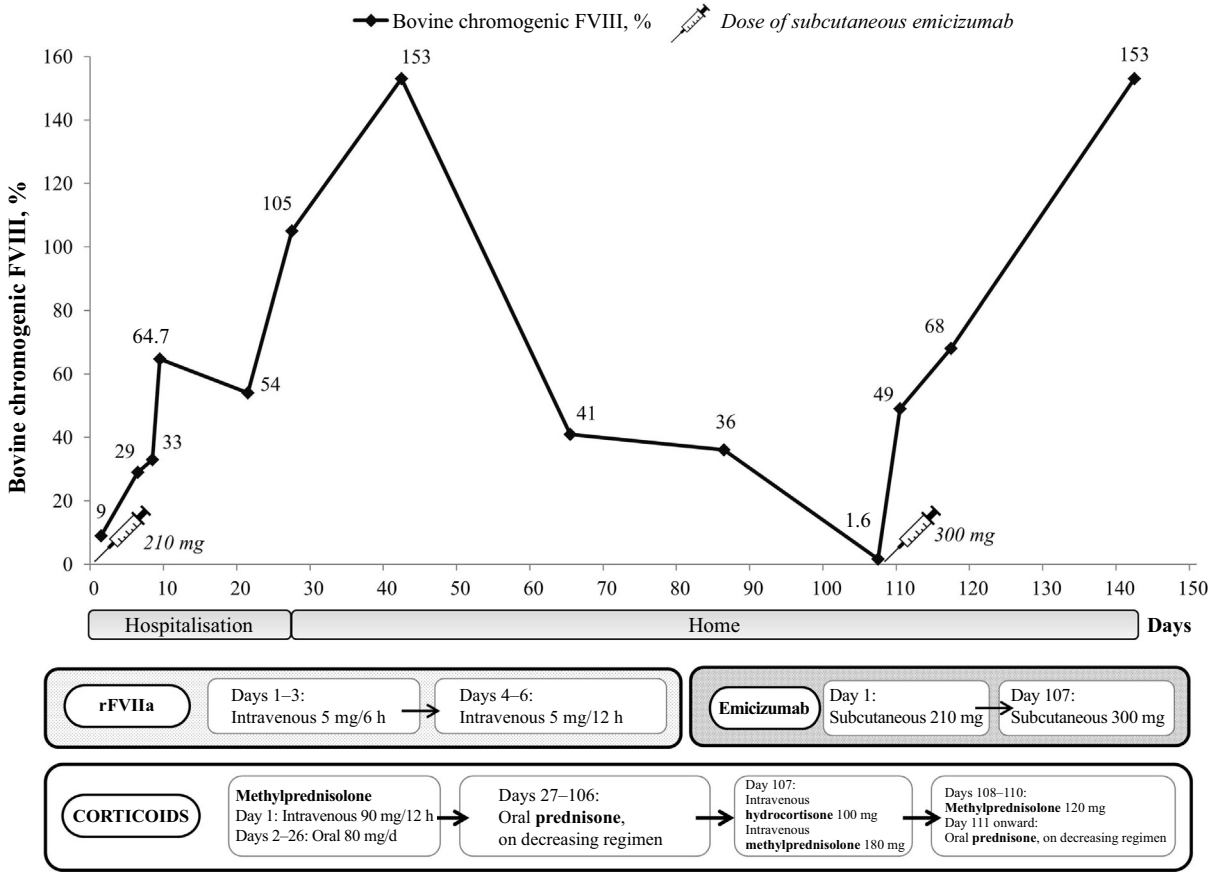

Fig. 1. Evolution of FVIII activity and summary of pharmacological treatment.

In view of the gradual improvement of the haematomas, good haemostatic performance from the start of treatment (FVIII activity: 105%), and the absence of new bleeding, the haematology and surgery departments agreed on hospital discharge after 2 months of hospitalisation (27 days after emicizumab administration). At discharge, treatment with oral prednisone 40 mg/d was indicated.

At the first follow-up visit at 15 days, the patient did not show bleeding symptoms—whether during toothbrushing or in urine or stool—or spontaneous haematomas. FVIII activity was 153.3% and emicizumab level 25.6 μg/mL (42 days post-administration), and so prednisone was reduced to 20 mg/d. In the periodic biweekly check-ups, a general improvement without bleeding was observed.

At a follow-up visit 2 months after discharge, a relapse related to non-adherence to corticosteroid treatment was detected, as evidenced by a large sublingual haematoma of several days' progression with odynophagia (FVIII activity: 1.6%). This situation was treated by the urgent administration of intravenous hydrocortisone 100 mg and a second dose of emicizumab 300 mg (4.3 mg/kg). Subsequently, a loading dose of intravenous methylprednisolone 180 mg was administered to be continued at home with oral methylprednisolone 120 mg/d. The patient showed favourable progress at the next appointment (72 h) and in the following appointments, which led to the corticosteroid regimen being reduced.

Four months after discharge, there were no further incidents related to haemostasis; FVIII activity was >100%, and so immunosuppressive treatment was suspended and monthly check-ups were scheduled.

Discussion

The management of AHA continues to be a challenge from the point of view of safety and efficacy. It requires safer agents at a dosage that reduces dependence on intravenous haemostatic therapy and enables outpatient monitoring. This approach has already been implemented in the setting of HA leading to a paradigm shift in how the disease is treated.

There are no studies on the potential role of emicizumab in AHA, nor is it authorised for such use in the Summary of Product Characteristics. The few published cases (none in Spain) suggest that it could be a safe and effective therapeutic option in achieving significant reductions in bleeding rates.[8,9] One of the main limitations to its use lies in the choice of dose and frequency of administration, given that there are still no recommendations for its use in this indication.[6] Although the risk of thrombosis has not been evaluated in these patients, the pivotal trials that led to the marketing of the drug found associations between thrombotic complications and the concomitant use of activated prothrombin complex, but not rFVIIa. Nevertheless, a clinical trial is in the recruitment phase and another has been completed with its results pending publication (NCT05345197, NCT04188639), which will undoubtedly shed light on its use in AHA.

In the present case, immunosuppression was performed with corticosteroids as monotherapy, rFVIIa was used as haemostatic therapy for 6 days, and 2 doses of emicizumab were administered at an interval of 105 days.[10] The use of emicizumab was safe, possibly contributed to shortening hospital stay, and involved less aggressive immunosuppressive treatment with few complications.

In conclusion, the off-label use of emicizumab in AHA appears to have a favourable efficacy and safety profile such that it could become a standard treatment in the future. Clinical trials and long-term follow-up are needed to assess the risk–benefit ratio and establish treatment guidelines.

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Author statement

The following authors have contributed to the preparation of the article regarding the conception and design of the clinical case described. M. Ángeles Ocaña Gómez and Jorge Esquivel Negrín were responsible for writing the article. Mario Ríos De Paz and M. Dolores De Dios García made a critical review of the article and offered relevant intellectual contributions. All 4 authors have approved the final version for its publication. Data collection was conducted by M. Ángeles Ocaña Gómez, Jorge Esquivel Negrín, Mario Ríos De Paz and M. Dolores De Dios García.

Presentations at congresses/scientific meetings

None declared.

Contribution to the scientific literature

We report a clinical case of acquired haemophilia A treated with emicizumab, the doses used, and the results.

The authorised indication of emicizumab in haemophilia A with inhibitors is the reference for its use; thus, all published clinical outcomes from other indications will valuable in developing the optimal treatment strategy.

Conflicts of interest

None declared.

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