

Emicizumab in acquired hemophilia A: a case report

Emicizumab en hemofilia adquirida A: a propósito de un caso

Antia Amoedo-Bastos, Manuel Rodríguez-López*, and Carmen Albo-López

Service of Hematology and Hemotherapy, Hospital Universitario Álvaro Cunqueiro, Instituto de Investigación Sanitaria Galicia-Sur (IISGS), EOXI Vigo, Vigo, Spain

Acquired hemophilia A (AHA) is a rare autoimmune coagulopathy, with an estimated incidence rate of 1 to 6 cases per million inhabitants per year, although this is probably underestimated because of the lack of diagnostic suspicion and the concomitant use of anticoagulants or antiplatelet agents in the affected population.¹ It predominantly affects elderly individuals, with a median age at diagnosis of 65 years and a biphasic distribution: a first peak in young women during the puerperium, and a second peak in individuals > 60 years, with no sex differences.¹ It is characterized by the development of neutralizing autoantibodies against coagulation factor VIII (FVIII), leading to spontaneous bleeding, which is often severe.

In more than 50% of cases, AHA is idiopathic. Identified underlying causes include systemic autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and Sjögren syndrome; solid tumors, including lung, prostate, colon, and pancreatic cancer; hematologic malignancies, such as non-Hodgkin lymphoma, chronic lymphocytic leukemia, and multiple myeloma; the postpartum period; and certain drugs, including penicillins, interferons, and fludarabine. Occasionally, cases related to infections, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have been described.^{1,2} Mortality associated with AHA ranges from 7 to 38% depending on the series, with most fatal events occurring within the first two months after diagnosis: uncontrolled bleeding

predominates in the early phases, whereas infections due to immunosuppressive (IS) treatment are the leading cause of late death.^{1,3}

The management of AHA is complex and challenging for several reasons. First, diagnosis is often delayed because bleeding is confused with bleeding secondary to anticoagulant or antiplatelet therapy. Second, bleeding risk does not correlate with inhibitor titer or residual FVIII levels, which makes individual risk stratification difficult. Third, the IS treatment required to eradicate the inhibitor, usually corticosteroids alone or in combination with cyclophosphamide or rituximab, entails relevant toxicity in an already frail population, with a high prevalence of comorbidities, opportunistic infections in up to 30% of cases, and infection-attributable mortality ranging from 15% to 47% in different registries.^{1,3,4}

Classically, hemostatic treatment is based on 2 categories of agents. Bypassing agents, recombinant activated factor VIIa (rFVIIa, NovoSeven®) and activated prothrombin complex concentrate (aPCC, FEIBA®), are the first-line standard, with efficacy of approximately 60–90%.^{1,2} In the Spanish registry,³ 70% of patients required hemostatic treatment, with rFVIIa being the most frequently used product (60.3% of cases), at a mean dose of 90 µg/kg per episode, a median of 15 doses, and a median duration of 7 days. Second, in patients with a low inhibitor titer (< 5 BU/mL), the use of high-dose human FVIII concentrates, up to 100–200 IU/kg, may be considered with the aim of

*Correspondence:

Manuel Rodríguez-López

E-mail: totsalcamp14@hotmail.com

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overcoming inhibition, although their efficacy is limited and the required doses are considerably high.^{1,2} In the EACH2 data series, the efficacy profile of FVIII concentrates was 34%, compared with 93% for bypassing agents.² Recombinant porcine factor VIII (susoctocog alfa, Obizur®) represents a valuable alternative, with 86% efficacy in the pivotal study, and is particularly useful when the inhibitor does not show significant cross-reactivity with the porcine antigen.¹ Finally, tranexamic acid may be used as an adjunct, especially in mucocutaneous bleeding or as the sole agent in minor bleeding, although its combination with aPCC increases thrombotic risk and should be assessed individually.^{1,5}

IS treatment for inhibitor eradication includes different drugs, either alone or in combination: corticosteroids, cyclophosphamide, and rituximab, an anti-CD20 antibody. In the Spanish registry,³ IS was administered in 96.6% of patients, with the combination of steroids and cyclophosphamide being the most widely used regimen (45.4%), and with a median time to complete remission of 49 days (IQR, 34–89 days). The main causes of death in these patients are usually infections, 9.9% in the Spanish registry, and uncontrolled bleeding, 3.3%, generally associated with very high inhibitor levels and low FVIII activity. In fact, an inhibitor titer ≥ 20 BU and FVIII activity $< 1\%$ are considered poor prognostic factors at diagnosis.^{2,3,4}

In recent years, evidence has emerged supporting the use of emicizumab in this condition, given the results shown in the management of congenital hemophilia with inhibitors.⁵ Emicizumab is a bispecific monoclonal antibody that replaces the function of FVIII in the tenase complex, restoring thrombin generation.⁶ Several reports have shown its efficacy in bleeding prophylaxis in patients with acquired hemophilia, reducing the need for bypassing agents.^{7–10} In some cases, it has been suggested that the use of emicizumab could reduce the need for IS by allowing time for natural immune tolerance to be achieved.⁷ Our objective is to report the experience with emicizumab in this context in a patient from our center. To this end, data were collected from the patient's electronic health record.

Case report presentation

A 90-year-old man was admitted for scheduled laparoscopic left colectomy in the setting of moderately differentiated colorectal adenocarcinoma (G2). The patient was receiving antiplatelet therapy with acetylsalicylic acid 100 mg/day because of a transient

ischemic attack in 2021, and this was not discontinued before surgery. In the immediate postoperative period, the patient presented with rectal bleeding and progressive anemia requiring multiple transfusions. The coagulation study showed prolonged activated partial thromboplastin time (aPTT), which corrected in the immediate mixing study, accompanied by decreased coagulation factors, except factor IX. Transfusion of fresh frozen plasma (FFP) was initiated at 10–15 mL/kg/day, without resolution of bleeding.

Of note, the FVIII inhibitors characteristic of AHA are time- and temperature-dependent in their inhibitory action; therefore, aPTT and mixing studies require prolonged incubation, 2 hours at 37 °C, to demonstrate their inhibitory effect.¹ In the case presented, the aPTT probably corrected in the initial mixing study because this prior incubation had not been performed, which delayed the diagnosis. Only after reviewing the past medical history and noting that the aPTT had been prolonged for approximately 6 months was the mixing study repeated with 2-hour incubation, showing a low-titer inhibitor against FVIII (4 BU).

Several reassessment colonoscopies showed only mild, diffuse bleeding in the anastomotic area, managed with clips and local hemostatic agents; however, rectal bleeding persisted. In this context, an oncologic patient with recurrent bleeding and previously prolonged aPTT, the possible presence of a coagulation inhibitor was suspected. Lupus anticoagulant was negative, and the remaining intrinsic pathway factors and von Willebrand factor were within the normal range. A diagnosis of probably secondary AHA was established in the context of the oncologic process. Chromogenic FVIII was higher than coagulant FVIII (29 vs. 69%), a characteristic finding of IgG4-type inhibitors in AHA.

To control active bleeding, in addition to discontinuing antiplatelet therapy, rFVIIa, recombinant activated factor VIIa, was indicated at 90 µg/kg every 2–3 hours, with progressive spacing until discontinuation after 5 days. The alternative use of high-dose human FVIII concentrate was not considered first choice because rFVIIa was available and, given that the inhibitor was time-dependent, the FVIII doses required to overcome inhibition would have been extremely high, 100–200 IU/kg or more, with little guarantee of efficacy.¹ Recombinant porcine factor VIII, susoctocog alfa, was not used in this case because it was not available at the center at that time. In parallel, IS was initiated with prednisone 1 mg/kg/day for 7 days, and compassionate use of

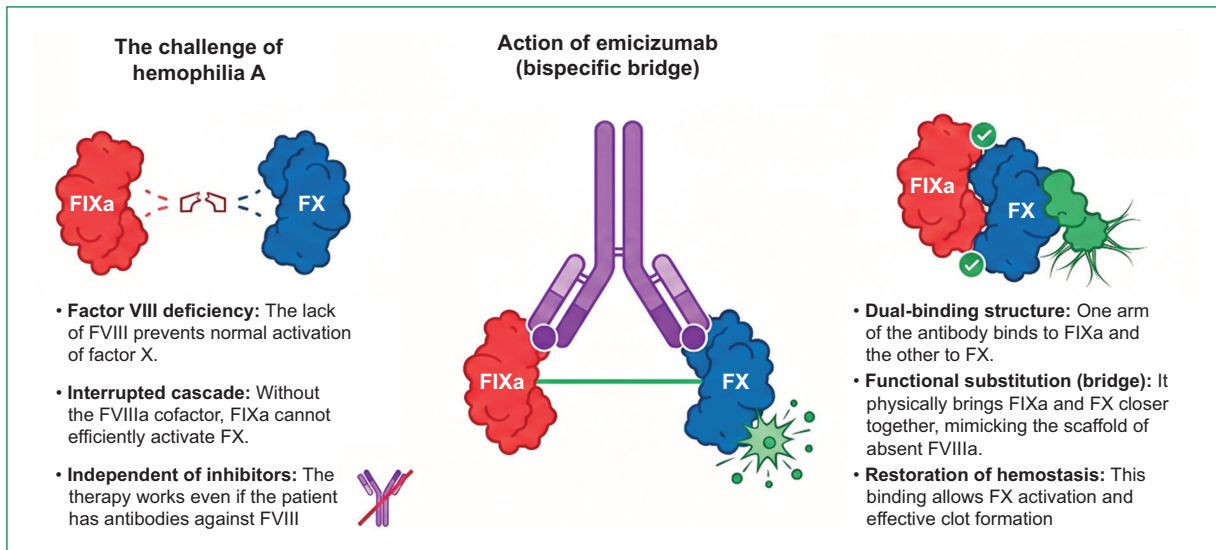


Figure 1. Mechanism of action of emicizumab (image generated with NotebookLM). FVIII: factor VIII; FX: factor X; FIXa: factor IV activated.

emicizumab, off-label, was requested for prophylaxis of inhibitor-associated bleeding (Fig. 1).

The regimen used was that described in the prospective AGEHA study, which allowed authorization of the drug in Japan for this indication¹⁰: dose 1 (D1), 6 mg/kg subcutaneously; dose 2 (D2), 3 mg/kg at 24 hours; and subsequently weekly maintenance at 1.5 mg/kg. Of note, there is no globally approved standard emicizumab dosing regimen for patients with AHA, and the regimen used in this case was derived from the above-mentioned prospective study and from the recommendations of the GTH working group.^{7,10} The high cost of emicizumab should also be mentioned, as it may limit its use in routine clinical practice, particularly in patients without clinically relevant bleeding and in whom the benefit-cost ratio is not clearly favorable.

When emicizumab was started and bleeding had ceased, the previous antiplatelet therapy was resumed. At 7 days, because of an increase in inhibitor titer (58 BU) and because the patient was elderly, the corticosteroid was discontinued and anti-CD20 therapy, rituximab, was started at 375 mg/m²/week for 4 weeks. The autoimmune profile showed positivity for anti-dsDNA antibodies (25.00 IU/mL), ANA (titer 1/80, homogeneous pattern AC-1), borderline antinuclear antibodies, anticardiolipin IgM antibodies (11.8 uMPL/mL), and positive anti-beta-2 glycoprotein I IgM antibodies (12.10 U/mL). Serology for hepatotropic viruses tested negative.

Despite treatment, the inhibitor titer peaked on day +14 (91 BU), indicating poor prognosis (> 20 BU). After

the start of emicizumab, no further bleeding occurred. The patient was discharged with outpatient hematology follow-up. As an intercurrent event, he attended the Emergency Department because of head trauma with a hematoma in the right supraciliary region and was treated with one dose of rFVIIa 90 µg/kg while awaiting the result of cranial computed tomography (CT), which showed no abnormalities. He had no other bleeding events. The inhibitor progressively decreased, reaching complete remission on day +60 (Fig. 2). At that time, emicizumab prophylaxis was discontinued, with initially weekly monitoring during the first month and progressive spacing thereafter, once the risk of relapse ranged from 12–18% depending on the initial regimen,² and was lower with anti-CD20 therapy. Controls have remained persistently negative, with inhibitor titer < 0.4 BU.

Discussion

AHA is a rare but potentially serious coagulopathy characterized by the sudden appearance of autoantibodies against FVIII, which is associated with severe bleeding and high morbidity and mortality, especially in elderly patients with comorbidities,^{1-3,11} such as the patient presented here. Our case illustrates the early use of emicizumab as prophylaxis after initial bleeding control with rFVIIa in a frail patient with active cancer.

This strategy is consistent with evidence from prospective studies such as GTH-AHA-EMI and AGEHA, in which emicizumab significantly reduced the incidence rate of new clinically relevant bleeding events

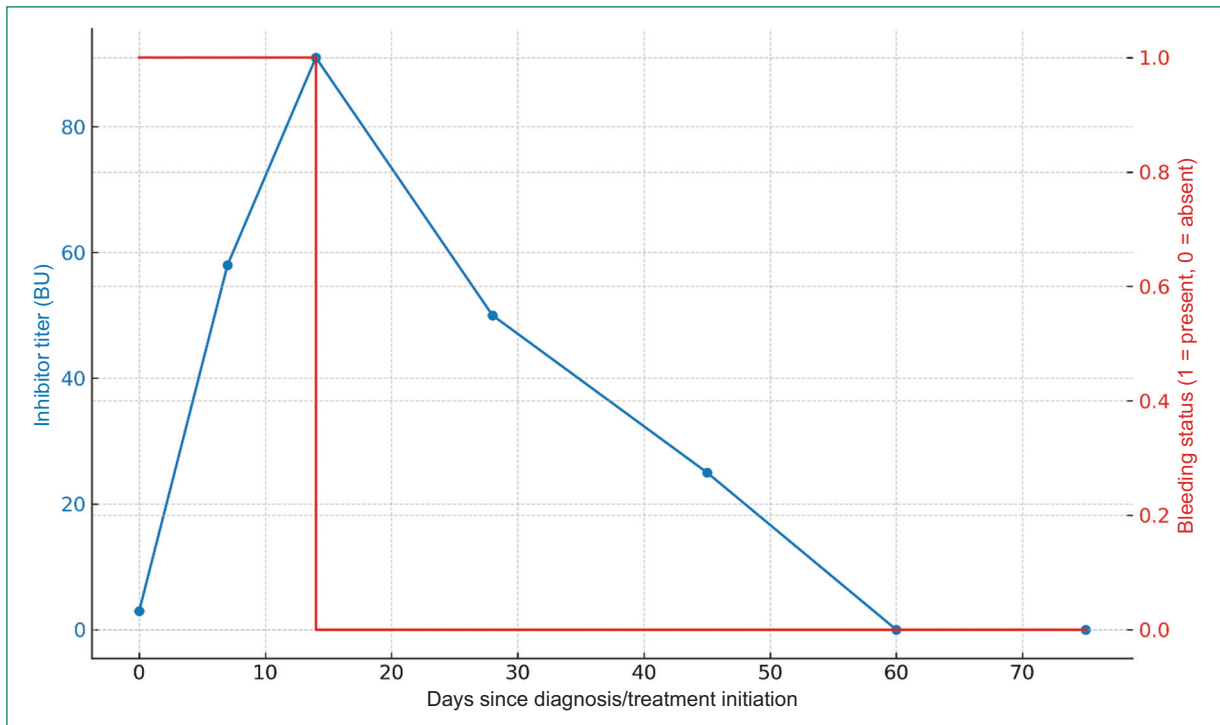


Figure 2. Evolution of inhibitor titer and bleeding in the patient.*

*Active bleeding is represented as 1 and absence of bleeding as 0. The inhibitor peaked on day +14 and remission was achieved on day +60.

and allowed IS to be deferred or even avoided in a substantial proportion of patients.^{7,10} In the GTH-AHA-EMI study, 75% of patients remained free from bleeding within the first 12 weeks without initial IS,⁷ whereas AGEHA documented the absence of major bleeding in both cohorts, even in patients without IS.¹⁰ In our case, emicizumab prevented hemorrhagic recurrence despite inhibitor titers as high as 91 BU and allowed reintroduction of the previous antiplatelet therapy without complications, findings consistent with recent series.^{12,13}

In addition, the time to complete remission, 60 days, was comparable to that reported in the Spanish registry, median 49 days; IQR, 34–89,³ and somewhat shorter than that observed in the GTH-AH 01/2010 registry, 79 days; IQR, 48–102,⁴ despite a more conservative IS strategy based on rituximab monotherapy. This reinforces the hypothesis that prophylaxis with emicizumab provides a “safety window” that makes it possible to reduce the intensity of IS, minimizing toxicity without compromising efficacy.

Of note, the conditions frequently associated with the development of AHA, such as advanced age, pregnancy and the puerperium, and cancer, are characterized per se by a higher baseline thrombotic risk,^{1,4} which should

be taken into consideration when initiating treatment with emicizumab. This drug may increase the risk of thrombosis in patients with AHA, especially when endogenous FVIII levels rise as a result of effective IS therapy, creating a state of relative hypercoagulability. In the present case, positivity for anticardiolipin IgM and anti-beta-2 glycoprotein I IgM added an additional thrombotic risk that justified close monitoring. Therefore, strict follow-up is recommended to detect thrombotic events early, such as deep vein thrombosis or stroke, especially in patients with preexisting cardiovascular risk factors.^{11,12} Once endogenous FVIII values reach or exceed 50%, treatment with emicizumab should be discontinued to prevent thrombosis.^{6,12}

In terms of overall safety, our patient tolerated treatment without relevant incidents, thrombotic events, or serious infections. The thrombotic risk described in the literature is mainly associated with the concomitant use of high-dose aPCC along with emicizumab,^{5,6} which reinforces the recommendation to prioritize rFVIIa or recombinant porcine FVIII in acute bleeding in patients receiving prophylaxis with emicizumab, avoiding aPCC in this context.^{6,11}

This approach raises several considerations. First, the current evidence comes from nonrandomized studies with small samples. Although the results are consistent, generalization requires caution. Second, the use of emicizumab in AHA is off-label in most countries, except Japan. This requires individualized indication supported by sound clinical and ethical criteria. Third, the optimal timing of initiation and the combination with IS have not yet been agreed upon. Studies such as AGEHA and GTH-AHA-EMI provide criteria, but formal guidelines integrating this strategy are still lacking.^{7,10}

In conclusion, this case supports the evidence backing the use of emicizumab as hemostatic treatment in acquired hemophilia A, especially in frail patients or those at high risk of complications derived from IS. Its ability to prevent new bleeding events, reduce the use of bypassing agents, and allow delayed initiation of IS could represent a paradigm shift in the initial management of this condition. Larger controlled clinical trials are required to confirm these findings and define standardized protocols.

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Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors followed the protocols of their

healthcare center/institution for access to data from medical records. Informed consent was obtained from the patients, and approval from the Ethics Committee was obtained. The recommendations of the SAGER guidelines were followed.

Declaration on the use of artificial intelligence.

The authors declare that ChatGPT-5 was used to create figure 1.

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