HEMOSTASIS AND THROMBOSIS

Review

Emicizumab in acquired hemophilia A: pros and cons of a new approach to the prevention and treatment of bleeding

Samantha Pasca[1], Ezio Zanon[2], Pier Mannuccio Mannucci[3], Flora Peyvandi[3,4]

[1]*Biological Sciences Department (DSB), Padua University Hospital, Padua, Italy;*
[2]*Hemophilia Center - General Medicine, Padua University Hospital, Padua, Italy;*
[3]*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center and Fondazione Luigi Villa, Milan, Italy;*
[4]*Università degli Studi di Milano, Department of Pathophysiology and Transplantation, Milan, Italy*

Emicizumab, a monoclonal bispecific antibody that mimics the function of activated factor VIII (FVIII), is currently licensed for prophylactic use in patients with congenital hemophilia A with and without inhibitors. Acquired hemophilia A (AHA) is a very rare bleeding disorder caused by the development of autoantibodies that inhibit FVIII activity in plasma; males and females are equally affected. Therapeutic options for patients with AHA currently include eradication of the inhibitor with immunosuppressive treatments and management of acute bleeding with bypassing agents or recombinant porcine FVIII. More recently, several reports described the off-label use of emicizumab in patients with AHA and a phase III study is ongoing in Japan. The aims of this review are to describe the 73 reported cases, and to highlight the advantages and disadvantages of this novel approach to the prevention and treatment of bleeding in AHA.

Keywords: *bispecific monoclonal antibody, off-label treatment, acquired bleeding disorders.*

INTRODUCTION

Emicizumab, a bispecific monoclonal antibody that mimics the procoagulant function of activated factor VIII (FVIIIa) by binding activated factor IX and factor X, plays an important role in the prophylactic treatment of patients with congenital hemophilia A with or without FVIII inhibitors[1]. Acquired hemophilia A (AHA) is a very rare bleeding disorder that equally affects males and females, with an estimated prevalence of 1.5 cases per million patient years. It is caused by the development of autoantibodies that inhibit FVIII activity in plasma. In almost half the cases, AHA is secondary to cancer, autoimmune diseases, and infections. It frequently occurs in elderly people, with an additional peak in women at the time of pregnancy and puerperium. The dual goal of treatment is the control of the bleeding and autoantibody eradication. FVIII bypassing agents and recombinant porcine FVIII (rpFVIII) are first-line therapies at the time of bleeding, and immunosuppressive drugs are concomitantly administered in order to attempt to eradicate the inhibitory autoantibody and restore plasma FVIII levels[2]. Several recent reports have described the off-label use of emicizumab in patients with AHA, and a phase III study (AGEHA) is ongoing, with preliminary data already available[3]. In this scenario, we collected and

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Correspondence: Pier Mannuccio Mannucci
e-mail: piermannuccio.mannucci@policlinico.mi.it

reviewed the available literature on this topic, with the purpose of highlighting the advantages and disadvantages of this novel approach to the management of AHA.

METHODS

This review was designed according to the "Preferred reporting items for systematic reviews and meta-analyses" (PRISMA) model[4]. A literature search included clinical studies, case reports, reviews, abstracts, and all scientific articles concerning AHA treated with emicizumab available on PubMed up to December 2022. The key terms "acquired hemophilia A", "acquired hemophilia A", "emicizumab" were used for the search, linked with the Boolean operator AND to terms such as "treatment" and "therapy". Only the titles and/or abstracts of the articles were considered in the search. In order to be included in this review, results had to meet the following criteria: 1) articles/abstracts concerning patients with AHA treated with emicizumab; 2) articles/abstracts written in English. Thus, a total of twelve manuscripts and six abstracts dealing with this topic were considered for this review, with the main findings summarized in **Table I**.

RESULTS

Prophylaxis of bleeding

Emicizumab was used as prophylaxis by a number of authors after the control of bleeding had been obtained with FVIII bypassing agents.

In an early report in 2019[5], Möhnle *et al*. described the case of an 83-year-old man diagnosed with AHA, with multiple comorbidities (**Table I**) and on long-term treatment with direct oral anticoagulants. Initially he was successfully treated with rpFVIII for bleeding and corticosteroids for immunosuppression, but owing bleeding recurrence and an increase in inhibitor titer, rpFVIII was replaced with recombinant activated factor VII (rFVIIa). Since bleeding persisted despite the decrease of the inhibitor titer, emicizumab was administered at an initial dose of 3.0 mg/kg/week followed by additional weekly doses of 1.5 mg/kg. This treatment was continued for a total of 36 days after which it was possible to discharge the patient, with no further bleeding or thrombotic complications.

Al-Baana *et al*.[6] reported the case of an elderly woman with atrial fibrillation on anticoagulant therapy and a recent history of gastrointestinal bleeding secondary to warfarin who, after anticoagulant discontinuation, was admitted to hospital for anemia and multiple hematomas. Plasma FVIII activity <1% and inhibitor titer >100 BU led to a diagnosis of AHA. Initially treated with activated prothrombin complex concentrate (aPCC) 50 IU/kg every 12 hours (h) for 2 weeks with a prompt control of bleeding, at discharge she was started on prophylaxis with emicizumab, initially at a dose of 3.0 mg/kg/week for one month followed by 1.5 mg/kg/week for another month. No further bleeds or adverse events were recorded.

Hess *et al*.[7] reported the case of a 91-year-old man with several concomitant diseases (**Table I**) admitted to hospital for anemia due to macroscopic hematuria. After being diagnosed with AHA (FVIII level <1%, inhibitor titer 44 BU/mL), he was treated with rFVIIa 90 μg/kg every 2 h for 24 h, which promptly stopped the hematuria. Following the onset a week later of an ileo-psoas hematoma, rFVIIa was restarted and bleeding stopped again. At hospital discharge this bypassing agent was replaced by prophylaxis with emicizumab at a loading dose of 3.0 mg/kg/week for four weeks and a maintenance dose of 1.5 mg/kg every two weeks. The patient was monitored for six months; there were no bleeding or adverse events.

Dane *et al*.[8] reported the case of a 72-year-old man with a history of bullous pemphigoid associated to AHA with a high-titer FVIII inhibitor refractory to multiple immunosuppressive regimens. To control acute bleeding, he was initially treated with aPCC, which was then continued as prophylaxis owing to the persistence of the bleeding tendency. After two years of this continued regimen, the patient was hospitalized for chest pain and non-ST-segment elevation myocardial infarction, and a percutaneous coronary intervention (PCI) was carried out under the cover of aPCC, continued at discharge as bleeding prophylaxis. After 15 weeks, he was rehospitalized for re-stenosis despite dual antiplatelet treatment. A drug-eluting stent was used under rpFVIII cover followed by continuous prophylaxis, first with aPCC and then with emicizumab 3.0 mg/kg/week together with dual anti-platelet treatment. The patient underwent a second PCI with no events to report and was transitioned to prophylaxis with emicizumab 1.5 mg/kg/week for a month. Follow-up at five months recorded no hemorrhage or cardiac event.

Chen *et al*.[9] described 4 patients with AHA and multiple comorbidities (**Table I**). Following hospitalization for acute

Table I - *Manuscripts and abstracts under review, and characteristics of the 73 patients reported and their management*

Reference	Patients	Co-morbidities	Emicizumab (dose/timing)	Immunosuppression	Previous treatments	Outcomes
Shima *et al.*, 2022[3] Phase III study	12 pts	No information	6 mg/kg (day 1), 3 mg/kg (day 2) + 1.5 mg/kg/wk (from day 8 onwards)	Yes, not specified	None	10/12 bleeding stopped, no AE. 1 DVT 5 minor bleeds in 2 pts
Möhnle *et al.*, 2019[5]	1 M, 83 y	Heart failure, atrial fibrillation, chronic kidney disease, previous VTE events	3.0 mg/kg (one dose) + 1.5 mg/kg for two doses (day 7 and day 20 after the first dose)	CS, RTX, IG	rpFVIII, rFVIIa PCC, FXIII concentrate, fibrinogen	Bleeding stopped after emicizumab, no AE.
Al-Banaa *et al.*, 2019[6]	1 F, 87 y	Atrial fibrillation	3.0 mg/kg/wk (4 wks) + 1.5mg/kg/wk (at least two months)	No information	aPCC	Bleeding stopped, no AE
Hess *et al.*, 2020[7]	1 M, 91 y	Atrial fibrillation, mitral valve stenosis, prostate hypertrophy	3.0 mg/kg/wk (4 wks) + 1.5mg/kg/2wk (at least six months)	CS, cyclosporine	rFVIIa	Bleeding stopped, no AE
Dane *et al.*, 2019[8]	1 M, 72 y	Bullous pemphigoid, coronary artery disease, PCI	3.0 mg/kg/wk (4 wks) + 1.5mg/kg/wk (five months)	Multiple immunosuppressive medications	aPCC, rpFVIII	Bleeding stopped, no AE, second PCI
Chen *et al.*, 2021[9]	3 M, 1 F (mean age 66 y)	Multiple comorbidities (CVD, diabetes, MGUS, dementia)	3.0 mg/kg/wk (4 wks) + 1.5 mg/kg/wk (mean 22 doses)	RTX (all patients) + CS (1 M patient) + cyclophosphamide (1 M patient and 1 F patient)	rpFVIII (all patients) + rFVIIa (1 F patient)	Bleeding stopped, no AE
Yates *et al.*, 2022[10]	1 M 83 y	Atrial fibrillation, low grade lymphoproliferative disorder	Not specified	CS, cyclophosphamide, RTX	rFVIIa aPCC	Bleeding stopped (multiple RBC transfusions), no AE
Escobar *et al.*, 2020[11]	1 M, 90 y 1 F, 57 y	Multiple co-morbidities	M - Texas protocol: 1.5 mg/kg/wk (two doses) + 1.5mg/kg/wk (21 days) F - standard protocol: 3.0 mg/kg/wk (4 wks) + 1.5mg/kg/wk	Not available	No information	Bleeding stopped, no AE
Gelbenegger *et al.*, 2022[12]	1 M, 75 y	Covid-19, hypertension, hyperlipidemia and an infrarenal aortic aneurysm. Previous STEMI	3.0 mg/kg/wk (3 wks) + 1.5 mg/kg every 2–4 weeks until complete remission	CS	rFVIIa	Bleeding stopped, no AE
Hansenne and Hermans, 2021[13]	1 M 73 y 1 M 93 y	Gout, hypertension, prostate cancer	3.0 mg/kg/wk + 6.0 mg/kg once 3.0 mg/kg/wk (4 doses) + 3.0 mg/kg/2wk (4 doses)	CS, cyclophosphamide, RTX	rFVIIa	Bleeding stopped, no AE
Al-Banaa *et al.*, 2021[14]	1 M 79 y	Rheumatoid arthritis, diabetes atrial fibrillation	3.0 mg/kg/wk (4 wks) + 3.0 mg/kg/2wk 1.5mg/kg/2wk (reduced after DVT)	CS	rpFVIII	Bleeding stopped, an asymptomatic DVT
Knöbl *et al.*, 2021[15]	6 M, 6 F (median 74 yrs)	Multiple co-morbidities (cancer, neurological disorders, gastrointestinal diseases, etc.)	3.0 mg/kg/wk (2-3 doses) + 1.5 mg/kg/3wk	10/12 CS, 12/12 RTX, 1/12 cyclophosphamide	rFVIIa	Bleeding stopped, a minor stroke during emicizumab with concomitant rFVIIa. One death

Continued on next page

Table I - *Manuscripts and abstracts under review, and characteristics of the 73 patients reported and their management (continued from previous page)*

Reference	Patients	Co-morbidities	Emicizumab (dose/timing)	Immunosuppression	Previous treatments	Outcomes
Knöbl *et al.*, 2022[16]	20 pts (11 M, 9 F) (median age 79 y)	No information	3 mg/kg/wk (4 wks) + 1.5 mg/kg/2-4 wks intervals	CS, RTX	rFVIIa	Bleeding stopped, no AE
Latef *et al.*, 2022[17]	1 F, middle-aged	HIV	3.0 mg/kg/wk (4 wks) + 1.5mg/kg/wk	CS, cyclophosphamide	BPA (AHA refractory)	Bleeding stopped, no AE
Flommersfeld *et al.*, 2019[18]	1 F 21 y	Multi-site autoimmune disease	3.0 mg/kg/wk (4 wks) + 1.5 mg/kg/wk	CS, cyclophosphamide, monoclonal antibodies	rFVIIa ITI	Bleeding initially stopped, no AE. Bleeding after dental extraction
Crossette-Thambiah *et al.*, 2022[19]	1 F	Post-partum, SARS-CoV-2 vaccination	3.0 mg/kg/wk (4 wks) + 3.0 mg/kg/2 wks	CS, azathioprine	rpFVIII, BPA	Bleeding stopped, no AE
Happaerts and Vanassche, 2022[20]	1 M 75 y	Bullous pemphigoid, SARS-CoV-2 vaccination	3.0 mg/kg two doses	CS, RTX	rFVIIa (concomitant)	Bleeding stopped, no AE
Chen *et al.*, 2022[21]	11 pts (5 M, 6 F) (median age 77 y	Multiple concomitant diseases	3.0 mg/kg/ week (4 weeks)	RTX	6 rFVIIa	Bleeding stopped, no AE One bleeding relapse

M: male; F: female; aPCC: activated prothrombin complex concentrate; AE: adverse events; AHA: acquired hemophilia A; BPA: unspecified bypassing agents; CS: corticosteroids; CVD: cardiovascular disease; DVT: deep vein thrombosis; FXIII: factor XIII; rFVIIa: recombinant activated factor VII; rpFVIII: recombinant porcine factor VIII; HIV: human immunodeficiency virus; IG: intravenous immunoglobulin; INH: inhibitor; ITI: immune tolerance induction; MGUS: monoclonal gammopathy of undetermined significance; PCI: percutaneous coronary intervention; RBC: red blood cells; RTX: rituximab; STEMI: ST-elevation myocardial infarction; VTE: venous thromboembolism; y: years.

bleeding they were first treated with rpFVIII and then, following the onset of anti-porcine FVIII antibodies, with rFVIIa and rituximab for immunosuppression with a satisfactory response. Prior to hospital discharge, all cases were put on long-term prophylaxis with emicizumab, 3.0 mg/kg/week for 4 doses followed by 1.5 mg/kg/week (22 doses). Only one of them required further hospitalization due to a traumatic bleeding event that was promptly resolved; no thromboembolic episodes or other adverse events were reported.

Yates *et al.*[10] described an 83-old-man with comorbidities (**Table I**), who was first seen as an outpatient because of fatigue attributed to anemia; he was given one unit of red blood cells (RBC). A few days afterwards, he was hospitalized due to an abdominal wall hematoma and large ecchymoses in the lower limbs, such that AHA was suspected. This was confirmed by lab tests, and a combined treatment of rFVIIa, tranexamic acid, prednisone, and cyclophosphamide was started. However, bleeding continued, with a decline in hemoglobin (Hb). Tranexamic acid was then stopped and replaced with aPCC; cyclophosphamide was also stopped owing to thrombocytopenia and rituximab was started. rFVIIa was discontinued once a stable Hb had been achieved. aPCC dosage was reduced and ultimately stopped when he developed atrial fibrillation. Prophylaxis of bleeding recurrence with emicizumab was initiated at hospital discharge, but 5 days later he was re-admitted with an altered mental status, left gluteal and thigh hematomas, orthostatic hypotension, and a drop in Hb, and rFVIIa was resumed. The patient was ultimately discharged and maintained on emicizumab prophylaxis 1.5 mg/kg every two weeks for 224 days, with no reported bleeding recurrence or thromboembolic events.

Escobar *et al.*[11] described two cases: a 57-year-old woman and a 90-year-old man. They were treated with two different dosage regimens of emicizumab: the standard protocol (a loading dose of 3.0 mg/kg/week for four doses followed by a maintenance of 1.5 mg/kg/week) and the so-called Texas protocol (a loading dose of 1.5 mg/kg/week for two weeks and maintenance with 1.5 mg/kg once every 21 days). Both regimens were effective in preventing bleeding and there were no apparent safety concerns, although no additional data are available.

Gelbenegger *et al.*[12] described a case of a 75-year-old male with Covid-19 and a previous history of ST-elevation myocardial infarction with coronary stenting, hypertension, hyperlipidemia, and an aortic aneurysm on dual antiplatelet treatment. He was admitted for pain in the left groin that revealed an ileus muscle hematoma. Dual antiplatelet therapy was temporarily stopped, but bleeding continued. A diagnosis of AHA was then made, and the patient was first put on prophylaxis with rFVIIa, followed by emicizumab 3.0 mg/kg/week for six weeks and 1.5 mg/kg every 2-4 weeks until bleeding stopped. No subsequent bleeding or thromboembolic events were reported. Antiplatelet treatment with clopidogrel was restarted as soon as the FVIII level exceeded 50%[12].

Treatment of acute bleeding

Emicizumab as second-line treatment of acute bleeding was described in a small number of manuscripts and abstracts.

Hansenne and Hermans[13] reported the case of a 73-year-old man with several co-morbidities. After two unsuccessful approaches, first with RBC units and then with rFVIIa, emicizumab was used to stop bleeding. No further bleeding or adverse events were reported.

Al-Banaa *et al.*[14] described a 79-year-old man with multiple comorbidities (**Table I**), including atrial fibrillation on anticoagulant treatment (apixaban 2.5 mg/bid), type 2 diabetes, and rheumatoid arthritis. Admitted to hospital for acute muscle and skin bleeding with anemia, he was first treated with RBC and rFVIIa with no clinical response. After AHA had been diagnosed (FVIII activity <1%; inhibitor titer of 627 BU/mL), treatment with rpFVIII and corticosteroids was started. Bleeding stopped in spite of the development of inhibitory antibodies against porcine FVIII, and the patient was discharged. Two weeks later, new hematomas appeared, and the inhibitor titer had risen to 749 BU/mL. Owing to a difficult intravenous access and a complex domestic situation during the Covid-19 pandemic, subcutaneous emicizumab was initiated as second-line strategy with the goal of first treating and then preventing bleeds (3.0 mg/kg/week for four weeks, followed by 3.0 mg/kg every two weeks). Bleeding stopped, but the patient experienced an asymptomatic non-occlusive proximal deep vein thrombosis in the left leg, leading to the anticoagulant that had previously been stopped being restarted and the emicizumab maintenance regimen (1.5 mg/kg every two weeks) being reduced.

Knoebl *et al.*[15] described a case series of 6 men and 6 women with AHA and severe bleeding treated upfront with immunosuppressive therapies to eradicate the inhibitor (mean titer 22.3 BU/mL). Only 8 cases were treated upfront with bypassing agents, which were subsequently also administered to the 4 remaining cases. Due to insufficient clinical responses and poor control of bleeding, emicizumab was started in all cases with a loading dose of 3.0 mg/kg/week for four weeks, maintained with two or three additional doses, and then followed by a dose reduction to 1.5 mg/kg for four weeks until plasma FVIII levels exceeded 10% following immunosuppression. Emicizumab was effective in stopping bleeding in all cases. However, a 79-year-old female developed a minor stroke on day 16 after starting emicizumab during a concomitant treatment with rFVIIa (90 µg/kg) and a male patient died albeit for causes related to his pre-existing clinical condition. An update of this case series enlarged to 20 patients was reported, confirming the previous findings[16].

The role of emicizumab as second-line therapy of acute bleeding was also reported by Latef *et al.*[17]. They described the history of a middle-aged woman with HIV who, after being hospitalized multiple times for AHA unresponsive to the treatment of bleeding with bypassing agents, was started on emicizumab, with the combined goal of resolving the acute bleeding concern and providing continuous prophylaxis. Bleeding stopped, the patient did not require hospitalization over the next three years of follow-up, and no adverse events were reported.

The case of a 21-year-old woman with a history of multi-site autoimmune disease was reported by Flommersfeld *et al.*[18]. First diagnosed with AHA following uncontrolled bleeding after minor skin surgery, she was treated with rFVIIa. All subsequent immunosuppressive treatments failed to eradicate the autoantibody and, due to persistent bleeding, rFVIIa was continued. An attempt was then made to induce immune tolerance with a combination of immunoadsorption, intravenous immunoglobulins, immunosuppression, and high-dose FVIII replacement. However, due to the recurrent bleeding, a new course of rFVIIa was started. Six months later, the patient was switched to prophylactic emicizumab at the conventional

dosage for congenital hemophilia. Bleeding was resolved and no further treatment was necessary until, a couple of months later, bleeding occurred following a dental extraction which required treatment with rFVIIa for one week.

Hansenne and Hermans[13] reported the first-line use of emicizumab for the acute treatment of bleeding in a 93-year-old man with metastatic adenocarcinoma hospitalized with multiple hematomas due to AHA (FVIII 1%; FVIII inhibitors 11.0 BU/mL). On admission, he was treated with methylprednisone and emicizumab 3.0 mg/kg/week for four doses, followed by 3.0 mg/kg every two weeks for a total of four additional doses. No bleeding or thromboembolic events were reported during follow-up.

Crossette-Thambiah[19] described 3 cases that occurred in the post-partum period after BNT162b2 (Pfizer, New York, NY, USA) SARS-CoV-2 vaccination. Two of the women had a complete response after treatment with by-passing agents and corticosteroids, but the third was refractory to such multiple medications as by-passing agents, rpFVIII, corticosteroids, and azathioprine. In this patient, emicizumab 3.0 mg/kg weekly for four weeks followed by 3.0 mg/kg every two weeks was then started, bleeding stopped, and during the next 10 months no thrombotic events were observed.

Happaerts and Vanassche[20] reported a case of AHA in a 75-year-old-man that occurred after Vaxzevria ChAdOx1-S SARS-CoV-2 (AstraZeneca, Cambridge, UK) vaccination with the concomitant relapse of bullous pemphigoid. A combined treatment with rFVIIa, rituximab, methylprednisolone, and emicizumab 3.0 mg/kg/week for two doses was started with the goal of stopping multiple hematomas and of eradicating the autoantibody.

A series of 11 patients (5 males and 6 females) treated with emicizumab and rituximab was reported by Chen *et al.*[21]. Eight of them had bled in multiple sites and 6 had previously been treated with rFVIIa, while emicizumab was immediately started as first-line therapy in 5. Bleeding stopped and 8 cases achieved inhibitor eradication. During a median follow-up of 13.9 months, only one patient bled but no thrombotic, microangiopathic nor infectious complications were recorded.

Phase III clinical trial

All the data reported so far are from case reports or case series in which emicizumab had been used off-label. Shima *et al.*[3] presented the preliminary results of the first multicenter, single-arm, phase III clinical trial (AGEHA) carried out in Japan to investigate safety, efficacy, pharmacokinetics and pharmacodynamics after administration of emicizumab in AHA. Their early analysis involved 12 patients on unspecified immunosuppression who were treated with emicizumab as prophylaxis at 6.0 mg/kg on day 1, 3.0 mg/kg on day 2, and then at 1.5 mg/kg/week from day 8 onwards. Emicizumab was discontinued when FVIII levels rose above 50%. Overall, 5 bleeds occurred during prophylaxis, but none of them was considered a major episode, in contrast to as many as 27 bleeds in the historical period before emicizumab. Furthermore, one patient experienced an asymptomatic deep vein thrombosis. Shima *et al.*[3] stated that these data suggested a favorable risk-benefit profile for emicizumab in AHA, but that additional data are warranted. Following the results of the AGEHA study, in June 2022 the Japanese Ministry of Health, Labor and Welfare chose to extend the approval of emicizumab to include its prophylactic use to prevent or reduce bleeding in patients with AHA, that in Japan is designated an intractable disease. Interestingly, the dosage regimen used (6 mg/kg on day 1, 3 mg/kg on day 2, and then 1.5 mg/kg weekly) differs from that approved for congenital hemophilia A, perhaps with the goal of accelerating the achievement of a steady state of the medication in the circulation and thus an earlier clinical response. An update of this study was recently presented in abstract form confirming the previously reported findings[22]. Three patients who had initially been ineligible to start immunosuppressive therapy had completed the trial and only one of them reported a minor adverse event related to emicizumab. Taken together, no serious events (including thrombosis and bleeding) were described, nor were there any modification or discontinuation of emicizumab. No anti-drug antibodies were detected[22].

DISCUSSION

Our review of these reports indicates that short- or long-term prophylaxis aimed at preventing bleeding appears to be the main clinical situation for a favorable use of emicizumab in patients with AHA, because all reports, including the AGEHA, demonstrated that this medication used at various dosage regimens was efficacious in the prevention of bleeding. Today there are still no specific

recommendations for treating patients with AHA with regards to the adoption of prophylaxis in order to prevent bleeding episodes when immunosuppression has not yet restored plasma FVIII levels. However, a few reports did indicate that aPCC, started soon after an acute bleeding episode, prevented recurrences[23,24]. In contrast to aPCC, emicizumab administration is subcutaneous, thus favoring prophylactic treatment at home. Furthermore, the possibility of obtaining a therapeutic steady state thanks to the achievement of a constant drug concentration in the circulation should allow AHA patients to attain hemostatic competence when endogenous FVIII activity is still low and there is a high risk of bleeding before immunosuppression is achieved.

The use of emicizumab as second-line of treatment of acute bleeds or as a rescue approach may be a therapeutic option in patients presenting before eradication of FVIII inhibitor when they develop frequent and/or life-threatening bleeds. Overall, this review identified 6 cases using this monoclonal antibody as first therapeutic choice. Other drugs are authorized and largely used for the primary treatment of acute bleeding in AHA, i.e., FVIII bypassing agents and rpFVIII, because they are immediately able to stop bleeding with no need to wait until emicizumab becomes effective. Recombinant porcine FVIII has the additional advantage of being monitored in the lab by means of FVIII assays.

On the other hand, it must be pointed out that the conditions frequently associated with the occurrence of AHA, i.e., older age, pregnancy and puerperium, and cancer, are characterized by an increased risk of thrombosis, and this must be taken into consideration. Therefore, patient management should be personalized, and the most suitable approach with the least risk adopted. The high thromboembolic risk associated with the treatment of AHA patients had previously been highlighted by the EACH2 study[25] in which 4.8% of thromboembolic episodes developed among patients treated with aPCC and 2.9% in those treated with rFVIIa; no thrombotic events were reported with the less frequently used rpFVIII[26,27]. During the pivotal post-marketing studies on emicizumab in congenital hemophilia A, 13 confirmed episodes of arterial or venous thrombosis (VTE) and 4 of thrombotic microangiopathy (TMA) were described[28]. Six of them (4 TMA; 2 VTE) occurred during the concomitant use of aPCC and 3 after the application of intravascular devices. Furthermore, in the context of the post-marketing surveillance of emicizumab conducted by the license holder, among a total of 56 thrombotic complications in more than 11,400 cases treated in 100 different countries, 7 occurred in patients with AHA receiving off-label emicizumab[29]. In the present review, despite the limited number of cases reported so far (No.=73), 3 thromboembolic events (2 DVT and one minor stroke) were described, and a patient died during treatment with emicizumab, albeit for causes apparently unrelated to the medication.

Taken together, the conclusion to be made from this review is a word of caution for clinicians who plan to use emicizumab in AHA, considering the high risk of thrombosis in the most frequent categories of potentially treatable patients, i.e., older people, cancer, and women during pregnancy and puerperium. Particular attention should also be paid to monitor endogenous FVIII levels[3], because emicizumab should be discontinued to reduce the risk of thromboembolic events when, owing to successful immunosuppression, plasma levels reach or exceed 50%. Despite limited real-world data, and the need for caution and careful monitoring of the treated patients outlined in this review, emicizumab is seen to play a role among the therapeutic approaches available for AHA, and there are many reasons for using it, as summarized by Poston *et al.*[30]. In the USA-based experience, 32 hematologists responded to a questionnaire regarding their experience with the management of AHA. Overall, they had treated 358 patients over five years, 40 of them with emicizumab, almost all as second-line therapy. This medication was chosen for the convenience of its subcutaneous administration in comparison with other hemostatic agents given intravenously, because of an insufficient response to those agents, and for a desire to minimize the period of immunosuppression or in response to failed immunosuppression.

DISCLOSURE OF CONFLICTS OF INTEREST

SP and EZ: no conflict of interest. PMM: Member of the scientific board for the Bayer Awards. He has also received from Bayer, Kedrion, Roche and Werfen honoraria for lectures at educational symposia. FP: Advisory boards Sanofi, Sobi, Takeda, Roche, Biomarin. Educational meetings: Grifols, Roche.

REFERENCES

1. Holstein K, Albisetti M, Bidlingmaier C, Halimeh S, Heine S, Klamroth R, et al; 'Ständige Kommission Hämophilie' (Haemophilia board) of the German, Swiss Austrian Society for Thrombosis Haemostasis Research (GTH). Practical guidance of the GTH haemophilia board on the use of emicizumab in patients with haemophilia A. Hamostaseologie 2020; 40: 561-571. doi: 10.1055/a-1127-6476.
2. Kruse-Jarres R, Kempton CL, Baudo F, Collins PW, Knoebl P, Leissinger CA, et al. Acquired hemophilia A: updated review of evidence and treatment guidance. Am J Hematol 2017; 92: 695-705. doi: 10.1002/ajh.24777.
3. Shima M, Amano K, Ogawa Y, Yoneyama K, Ozaki R, Kobayashi R,et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis in patients with acquired hemophilia A: primary analysis results from a phase III study (AGEHA) [abstract]. Proceedings of the 30th Congress of the International Society on Thrombosis and Haemostasis; 2022: OC 40.2.
4. Moher D, Liberati A, Tetzlaff J, Altman DG, for the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009 Jul 21; 339: b2535. doi: 10.1136/bmj.b2535.
5. Möhnle P, Pekrul I, Spannagl M, Sturm A, Singh D, Dechant C. Emicizumab in the treatment of acquired haemophilia: a case report. Transfus Med Hemother 2019; 46: 121-3. doi: 10.1159/000497287.
6. Al-Banaa K, Alhillan A, Hawa F, Mahmood R, Zaki A, El Abdallah M, et al. Emicizumab use in treatment of acquired hemophilia A: a case report. Am J Case Rep 2019; 20:1046-1048. doi: 10.12659/AJCR.916783.
7. Hess KJ, Patel P, Joshi AM, Kotkiewicz A. Utilization of emicizumab in acquired factor VIII deficiency. Am J Case Rep. 20207; 21: e922326. doi: 10.12659/AJCR.922326.
8. Dane KE, Lindsley JP, Streiff MB, Moliterno AR, Khalid MK, Shanbhag S. Successful use of emicizumab in a patient with refractory acquired hemophilia A and acute coronary syndrome requiring percutaneous coronary intervention. Res Pract Thromb Haemost. 2019; 3: 420-423. doi: 10.1002/rth2.12201.
9. Chen SL, Ellsworth P, Kasthuri RS, Moll S, Ma AD, Key NS. Emicizumab reduces re-hospitalization for bleeding in acquired haemophilia A. Haemophilia 2021; 27: e585- e588. doi: 10.1111/hae.14335.
10. Yates SG, Webb CB, Sarode R, Ibrahim IF, Shen YP. Utilization of emicizumab in acquired hemophilia A: A case report. Transfus Apher Sci 2022; 61: 103457. doi: 10.1016/j.transci.2022.103457.
11. Escobar M, Aboshady I, Montanez N. Prophylactic potential of standard and modified emicizumab prophylaxis in 2 patients with acquired hemophilia: a case report [Abstract]. J Thromb Haemost 2020: PB0791.
12. Gelbenegger G, Traby L, Rahimi N, Knöbl P. Management of acquired haemophilia A in severe Covid-19: Haemostatic bridging with emicizumab to keep the balance between bleeding and thrombosis. Br J Clin Pharmacol 2023; 89: 908-913. doi:10.1111/bcp.15598.
13. Hansenne A, Hermans C. Emicizumab in acquired haemophilia A: about two clinical cases and literature review. Ther Adv Hematol 2021; 12: 20406207211038193. doi: 10.1177/20406207211038193.
14. Al-Banaa K, Gallastegui-Crestani N, von Drygalski A. Anticoagulation for stroke prevention after restoration of haemostasis with emicizumab in acquired haemophilia A. Eur J Case Rep Intern Med 2021; 8: 002984. doi: 10.12890/2021_002984.
15. Knoebl P, Thaler J, Jilma P, Quehenberger P, Gleixner K, Sperr WR. Emicizumab for the treatment of acquired hemophilia A. Blood 2021; 137: 410-419. doi: 10.1182/blood.2020006315.
16. Knöbl P, Thaler J, Jilma P, Quehenberger P, Gleixner K, Sperr W. Emicizumab for the treatment of acquired hemophilia A: an update of the Vienna experience [abstract]. Proceedings of the 30th Congress of the International Society on Thrombosis and Haemostasis 2022: PB0002.
17. Latef TJ, Bhardwaj P, Bilal M. Refractory acquired haemophilia A in a patient with HIV treated with emicizumab. Blood Coagul Fibrinolysis 2022; 33: 138-140. doi: 10.1097/MBC.0000000000001118.
18. Flommersfeld S, Slonka J, Bieberle I, et al. Successful control of bleeding with emicizumab in aquired haemophilia A: a case report [abstract]. Proceedings of the 63rd Annual Meeting of the Society of Thrombosis and Haemostasis Research; 2019: P01-1.
19. Crossette-Thambiah C, Arachchillage D, Laffan M. Post-partum acquired haemophilia A in the COVID era – building the case for emicizumab? [abstract]. Proceedings of the 30th Congress of the International Society on Thrombosis and Haemostasis; 2022: PB0007.
20. Happaerts M, Vanassche T. Acquired hemophilia following COVID-19 vaccination: case report and review of literature. Res Pract Thromb Haemost 2022; 6: e12785. doi: 10.1002/rth2.12785.
21. Chen EC, Gibson W, Temoczko P, Connell NT, Handin R, Parnes AD. Emicizumab for the treatment of acquired hemophilia A: Retrospective review of a single-institution experience. Haemophilia 2023; 29: 84-89. doi: 10.1111/hae.14664.
22. Nishiki H, Suzuki N, Kobayashi R et al. Efficacy and Safety of Emicizumab Prophylaxis in Patients with Acquired Hemophilia a Who Were Deemed Ineligible for Immunosuppressive Therapy: Additional Data from the Ageha Study [abstract]. Blood 2022; 140 (Suppl 1): OC1153.
23. Árokszállási A, Rázsó K, Ilonczai P, Oláh Z, Bereczky Z, Boda Z, et al. A decade-long clinical experience on the prophylactic use of activated prothrombin complex concentrate in acquired haemophilia A: a case series from a tertiary care centre. Blood Coagul Fibrinolysis 2018; 29: 282-287. doi: 10.1097/MBC.0000000000000716.
24. Zanon E, Pasca S, Siragusa S, Napolitano M, Santoro C, Mameli L, et al. Low dose of aPCC after the initial treatment in acquired haemophilia A is useful to reduce bleeding relapses: Data from the FAIR registry. Thromb Res 2019; 174: 24-26. doi: 10.1016/j.thromres.2018.12.006.
25. Knoebl P, Marco P, Baudo F, Collins P, Huth-Kühne A, Nemes L, et al.; EACH2 Registry Contributors. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). J Thromb Haemost 2012; 10: 622-631. doi: 10.1111/j.1538-7836.2012.04654.x.
26. Kruse-Jarres R, St-Louis J, Greist A, Shapiro A, Smith H, Chowdary P, et al. Efficacy and safety of OBI-1, an antihaemophilic factor VIII (recombinant) porcine sequence in subjects with acquired haemophilia A. Haemophilia 2015; 21: 162-170. doi: 10.1111/hae.12627.
27. Zanon E, Pasca S, Borchiellini A, Lodigiani C, Molinari AC, Ambaglio C, et al. Susoctocog-alfa (Obizur ®) in the treatment of nine elderly patients with acquired haemophilia A: an Italian multicentre real-world experience. Blood Transfus 2020; 18: 312-321. doi: 10.2450/2020.00006-20.
28. Lee L, Moreno K, Kuebler P, et al. Summary of thrombotic or thrombotic microangiopathy events in persons with hemophilia A taking emicizumab [abstract]. Proceedings of the National Hemophilia Foundation (NHF) Bleeding Disorders Virtual Conference 2020: Atlanta, USA; PB003.
29. Howard M, McKinley D, Sanabria F, Ko RH, Nissen F. Evaluation of the safety of emicizumab prophylaxis in persons with hemophilia A: An updated summary of thrombotic events and thrombotic microangiopathies [abstract]. Blood 2021; 138 (Suppl 1): 3186. doi: 10.1182/blood-2021-146147.
30. Poston J, Kruse-Jarres R. The use of emicizumab for acquired hemophilia A at US hemophilia treatment centers [abstract]. Proceedings of the 29th Congress of the International Society on Thrombosis and Haemostasis (ISTH) 2021: PB0431.