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Emicizumab in acquired haemophilia A: about two clinical cases and literature review

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***Abstract*:** Acquired haemophilia A (AHA) is a rare and severe haemorrhagic autoimmune disease caused by autoantibodies directed against factor VIII (FVIII). Treatment is based on two principles, including haemostatic control to compensate FVIII inhibition and eradication of inhibiting antibodies using immunosuppressive therapy. Rapid recognition and proper management are essential to avoid excess morbidity and mortality. Effective and safe treatments can be challenging, given that AHA patients are often elderly, with multiple comorbidities. Emicizumab, a bispecific antibody that mimics the action of FVIII, has proven effective in managing patients with congenital haemophilia, with or without inhibitors. Likewise, its mode of action suggests theoretical efficacy in AHA patients. We herein describe two AHA cases with comorbidities that were treated effectively using emicizumab combined with immunosuppressive therapy. We have also reviewed the current literature regarding the promising use of emicizumab in this indication.

Keywords: acquired haemophilia A, bypassing agents, emicizumab

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Introduction

With approximately 1.5 cases per million patients/year, acquired haemophilia A (AHA) is a rare haemorrhagic disease.[1] Its rapid recognition is nevertheless crucial. Until now, haemostatic treatment has consisted of using factor VIII (FVIII)-bypassing agents like recombinant human activated factor VII (rhFVIIa) or activated prothrombin complex concentrates (aPCCs) to control bleeding complications. Porcine factor VIII (pFVIII) represents a more recent and less widely used alternative.[2] Despite their haemostatic efficacy, these agents display several weaknesses, including their intravenous route of administration, short half-life requiring repeated injections, complex monitoring of haemostatic activity, potential thrombogenicity and high costs.[3,4]

Emicizumab is a recombinant, humanized, bispecific antibody that binds to FIXa and FX, thereby mimicking the cofactor action of FVIII. Emicizumab has become an integral part of the treatment arsenal for congenital haemophilia A. In addition, emicizumab has established itself as the reference standard for treating congenital haemophilia A patients with inhibitors against exogenous FVIII.[5–7] Its use in AHA patients has recently been described in several case reports[8–10] and series.[11,12] Herein, we report on two case studies of patients with newly diagnosed AHA, who were treated effectively and without any complications with emicizumab, and we also provide a literature review on the topic.

Case reports

Case 1

A 73-year-old patient was admitted to our institution after a fall at his home where he remained on the floor for another 48 h. He exhibited multiple skin haematomas, along with a large muscle and soft tissue haematoma of his left thigh. His medical history consisted of gout, essential hypertension and chronic alcohol consumption. He had no cardiovascular history, but thoracic–abdominal

and cerebral computer tomography (CT) scans revealed severe and diffuse atheromatosis, in addition to marked cerebral microvascular damage. The patient was poorly compliant and had been off medications (spironolactone, allopurinol, cetirizine) for several weeks.

Laboratory workup on admission revealed anaemia (haemoglobin: 7.2 g/dl), acute renal failure (creatinine: 3.99 mg/dl), elevated creatine phosphokinase (CPK: 822 IU/l) levels and isolated prolongation of activated partial thromboplastin time (aPTT) (>90 s). Upon admission, the patient's initial diagnosis was rhabdomyolysis. Thereafter, the patient was hospitalized for 4 days in the intensive care unit because of an acute coronary syndrome without ST-segment elevation, which was described as functional, secondary to anaemia. He then received 1-g tranexamic acid 3 times daily, and he was transfused with six units of red blood cells and five units of fresh plasma. As aPTT was still prolonged, further haemostatic investigations were carried out, revealing severe FVIII deficiency (<1%), presence of an inhibitor [15.2 Bethesda units (BU)] and absence of lupus anticoagulant, thereby confirming the AHA diagnosis. Treatment with 1-mg/kg methylprednisolone was initiated on day 5 following his admission.

On day 7, the patient was transferred to a tertiary centre where he received rituximab (375 mg/m^2, weekly, four doses in total) and cyclosporine (100 mg per day for 1 month). On day 11, overall 7-mg rhFVIIa was administered, owing to a sudden drop in haemoglobin levels, and haemodynamic instability as well, including hypotension, tachycardia and neurological deterioration, although no bleeding complications were shown on thoracic–abdominal CT scans. The patient was transfused with four additional units of red blood cells. The next day, treatment with emicizumab, which was obtained for compassionate use, was initiated at a dose of 3 mg/kg. Overall the patient received five emicizumab doses, meaning 4 times 3 mg/kg weekly and then 6 mg/kg once. After the first emicizumab injection, the patient did not experience any bleeding recurrence, and no further transfusions or rhFVIIa administrations were thus required. No thrombotic complications were observed. D-dimer concentration turned out to be high at emicizumab initiation, which was likely secondary to multiple haematomas. D-dimer levels were then monitored regularly, decreasing gradually. As expected with emicizumab, the aPTT falsely normalized after the first injection. The conventional aPTT measurement is indeed no longer interpretable in the presence of emicizumab and cannot reflect the haemostatic capacity of the patient. During follow-up, FVIII monitoring using chromogenic assays with human and bovine substrates showed the following concentrations: <1% on admission (human substrates), 12% (human substrates) and 3% (bovine substrates) after the initiation of emicizumab and 178% (human substrates) and 171% (bovine substrates) after eradication of the inhibitor. The patient was discharged from hospital on day 38. At the last follow-up consultation, which took place 75 days after treatment initiation and 28 days after last emicizumab injection, the patient was in good shape, without any further bleeding signs. Haemoglobin was at 13.4 g/l, aPTT was normalized and FVIII concentrations were within normal limits according to the assay methods (chromogenic assays using human and bovine reagents), with the inhibitor no longer detectable. Methylprednisolone dosing was then gradually reduced to 24 mg/day and then stopped. On note is that no underlying cause for AHA was found.

Case 2

A 93-year-old man was admitted to our institution for diagnostic workup of acute onset haemorrhagic diathesis. Clinical examination revealed multiple diffuse subcutaneous haematomas. The patient was known to be suffering from a metastatic prostatic adenocarcinoma, which was stabilized under enzalutamide, the prostatic-specific antigen (PSA) being negative; he was also affected by arterial hypertension. He lived autonomously at home. His chronic medications included aspirin, which had been stopped by his general practitioner a few days earlier, as well as bisoprolol, allopurinol, enzalutamide, gabapentin, lisinopril and pantoprazole. A deep-seated psoas haematoma was detected on CT scan. The blood tests documented a severe anaemia requiring rapid transfusion of three units of red blood cells, aPTT was prolonged to 79 s in isolation and FVIII was measured at 1% using one-stage aPTT and chromogenic assay with human reagents. The anti-FVIII antibody test was positive (titrated at 11 BU).

On admission day, emicizumab treatment was immediately initiated using a starting dose of 3 mg/kg concomitantly with methylprednisolone

(from day 1) as immunosuppressive treatment and 375-mg/m^2 rituximab (from day 2, weekly for four doses). Emicizumab was administered weekly at 3 mg/kg for 4 weeks and then every 2 weeks for four doses. After the first dose of emicizumab, no new bleeding events were observed, though a transfusion was repeated on day 4. No additional haemostatic agents were required, and the patient was discharged 8 days after admission. The methylprednisolone dose was rapidly reduced from 80 to 32 mg upon discharge. Outpatient follow-up was carried out in the haematological day hospital. The titre of the inhibitor decreased rapidly after initiation of immunosuppressive therapy and had completely disappeared within 3 months. FVIII was measured by chromogenic assay at 1% (human substrates) on admission, at 20% (human substrates) and 1% (bovine substrates) on emicizumab and 73% (human substrates) and 63% (bovine substrates) after eradication of the inhibitor. The patient was in remission when last seen at the 4-month follow-up visit, that is, 1 month after stopping emicizumab. The remaining small dose of methylprednisolone (4 mg/48 h) was then stopped.

Discussion and literature review

The development of anti-FVIII autoantibodies, also termed as AHA, is a rare cause of haemorrhagic diathesis.[1] However, this condition is responsible for the most commonly acquired inhibition of coagulation factors. In 50% of cases, an underlying cause can be identified, including, among others, autoimmune diseases like rheumatoid arthritis or systemic lupus erythematosus, cancers, drug reactions, pregnancy and postpartum. Half of the cases are idiopathic in nature.[1,13,14] The clinical presentation is generally dominated by mucocutaneous bleedings. Digestive, soft tissue, intracranial and postoperative haemorrhages are also possible. Unlike congenital haemophilia, intra-articular haemorrhages are rare in this setting. These bleeds can be severe and, thus, quickly become life-threatening.[14]

AHA diagnosis is based on the clinical presentation of haemorrhagic diathesis associated with marked and isolated elevated aPTT levels. The aPTT does not normalize following plasma mixing or phospholipid addition, in the absence of heparin therapy. FVIII activity is reduced. The FVIII inhibitor can be quantified using the Bethesda method, which is based on a dilution of the patient's plasma with normal plasma. BU is then defined as the amount of inhibitor capable of neutralizing 50% of FVIII contained in 1 ml of normal plasma. An enzyme-linked immunosorbent assay (ELISA) for FVIII inhibitors has been developed, as well.[15]

Apart from controlling a potential underlying cause, AHA treatment pursues two goals, including prevention of bleeding complications and removal of autoantibodies directed against FVIII. Haemostatic therapy is currently based on administering FVIII-bypassing agents like aPCC (FEIBA) or rhFVIIa (Novo Seven). Porcine FVIII (Obizur) is also employed in this indication, owing to commonly missing cross-reactivity of autoantibodies to porcine-derived FVIII. Using high-dose recombinant human FVIII is no longer recommended, even for patients with low inhibitor titres.[2,4] Emicizumab, a bispecific antibody directed against FIXa and FX and mimicking the action of FVIII, has revolutionized the treatment of congenital haemophilia owing to both its efficacy in bleeding prophylaxis and its ease of use. By analogy and considering the pathophysiological mechanisms, the use of emicizumab in AHA was judged promising.[16] Since 2019, several case reports[8–10] and case series[11,12] have been published describing the use of emicizumab in AHA [PubMed search – keywords: emicizumab / acquired haemophilia A – January 2021; American Society of Hematology (ASH) Meeting and Exposition presentations – December 2020] (Table 1).

In April 2020, Takeyama and colleagues published their data covering *ex vivo* emicizumab efficacy on standard coagulation tests. These authors first employed AHA-model plasma, meaning normal plasma preincubated with anti-FVIII monoclonal antibodies. Using a low-concentration tissue factor–triggered thrombin generation assay, they demonstrated that emicizumab increased thrombin generation in a dose-dependent manner. Their subsequent studies were conducted on plasma samples from 12 AHA patients prior to undergoing immunosuppression, and the authors demonstrated emicizumab to enhance clotting potential in all cases, with varying increases in thrombin generation.[16]

In 2019, three case reports described emicizumab efficacy as first-line treatment in AHA patients or in those refractory to conventional therapy,

Table 1. Review of relevant publications evaluating the use of emicizumab in AHA (January 2021).

Publications and references	Publication type	Patient(s) profile	Initial haemostatic treatment(s)	Emicizumab dose	Immunosuppressive treatment(s)	Outcomes
Takeyama and colleagues[16] (Japan) April 2020	*Ex vivo* study	–	–	–	Blood samples obtained prior to immunosuppression	*Ex vivo*, emicizumab improves the clotting potential in the plasma of patients with acquired haemophilia
Dane and colleagues[8] (UK) April 2019	Case report	Male, 72 years old AHA associated with bullous pemphigoid Refractory inhibitor, several lines of immunosuppressive treatment Symptomatic coronary artery disease, intrastent stenosis (after early stop of the double antiaggregation because of recurrent bleeding)	aPCC	3 mg/kg weekly for a month then 1.5 mg/kg weekly	Multiple prior immunosuppressive therapies: corticosteroids, rituximab, cyclophosphamide, cyclosporine, azathioprine, bortezomib, mycophenolate, cladribine and tacrolimus	After 4 weeks of treatment with emicizumab, percutaneous coronary intervention and placement of a pharmacoactive stent Double antiaggregation aspirin–clopidogrel No haemorrhagic or thrombotic complications at 5-month follow-up
Möhnle and colleagues[9] (Germany) April 2019	Case report	Male, 83 years old Multiple comorbidities AHA relapse Bleeding despite multiple haemostatic therapies, clinical deterioration	pFVIII rhFVIIa aPCC FXIII Fibrinogen	A dose of 3 mg/kg then 1.5 mg/kg for two doses (one on day 7 and one on day 20 after the first dose)	Corticosteroids Rituximab Intravenous immunoglobulins	Clinical stabilization and no further haemostatic therapy required after emicizumab therapy initiation Discharge from hospital possible Death a few weeks later without evidence of bleeding or thrombotic event (no autopsy)
Al-Banaa and colleagues[10] (USA) July 2019	Case report	Female, 87 years old First line of treatment	aPCC	3 mg/kg weekly for 1 month then 1.5 mg/kg weekly for at least 2 months	No information	Stable under aPCC at the time of introduction of emicizumab, progressive cessation of aPCC Discharge from hospital and outpatient follow-up, no haemorrhagic or thrombotic complications
Knoebl and colleagues[11] (Austria) August 2020	Case series	12 patients Median age: 74 years All patients: at least one comorbidity First line of treatment	rhFVIIa	3 mg/kg per week for two to three doses then 1.5 mg/kg every 3 weeks. Median of five doses (3–9)	Corticosteroids: 10 patients (1-mg/kg prednisone 1 week, then decrease the dose over 2 weeks) Cyclophosphamide: one patient (8 days) Rituximab: all	Efficient haemostatic treatment with the advantage of subcutaneous treatment, rapid discharge from hospital and a reduction in immunosuppression and side effects of the treatment One patient: Minor stroke during concomitant treatment with repeated dose rhFVIIa for invasive care, rapid recovery without sequelae
Chen and colleagues[12] (USA) November 2020 – ASH Meeting December 2020	Case series	8 patients	–	Four doses of 3 mg/kg, weekly Then 3 mg/kg every 2 weeks for one patient, not described for the other patients	Rituximab: all Corticosteroids: three patients (1-mg/kg prednisone for 10–14 days)	Efficient and safe for all patients aPTT normalization after one to two doses No recurrent bleeding except haematuria in a patient (local cause)

AHA, acquired haemophilia A; aPCC, activated prothrombin complex concentrate; aPTT, activated partial thromboplastin time; ASH, American Society of Hematology; FXIII, factor XIII; pFVIII, porcine factor VIII; rhFVIIa, recombinant human activated factor VII.

Table 2. Potential benefits of emicizumab therapy for the management of AHA.

Current treatment challenges in (AHA)	Potential benefits of emicizumab in AHA
• Risk of recurrent severe bleeding complications until inhibitor eradication	• Relatively fast prophylactic haemostatic efficacy
Classical FVIII-bypassing agents: • Need for intravenous access • Short half-life and need for repeated administrations • Need to individualize use of bypassing agents • Biological evaluation of efficacy requiring global coagulation assays (thrombin generation, ROTEM, etc.) • Thrombotic risk • No validated prophylactic strategy in patients with persistent inhibitor	Emicizumab • Subcutaneous administration • Weekly and then monthly administration possible • Standard use of a single bypassing agent in most cases • Shortening of aPTT reflects the action of emicizumab. Chromogenic assay with bovine FVIII needed for measurement of endogenous FVIII and inhibitor titration • No evidence of increased thrombotic risk based on available data, including high-risk patients • Suitable for prolonged and even long-term prophylaxis if necessary
• Morbidity and mortality related to immunosuppressive treatment(s)	• Possibility to consider an immunosuppressive treatment of reduced intensity and adapted to the patient's profile
• Prolonged hospital stays (need for intravenous access; repeated administrations of bypassing agents)	• Outpatient follow-up possible as soon as the patient is clinically stable
• Costs associated with prolonged hospitalization(s), repeated uses of bypassing agents (not predictable), complications related to immunosuppression	• Potential saving through reduced hospital stay duration, reduced complications and use of a single, predictable bypassing agent

AHA, acquired haemophilia A; aPTT, activated partial thromboplastin time; FVIII, factor VIII; ROTEM, rotational thromboelastometry.

without any secondary thrombotic or other major treatment-related complications (Table 1).

Two case series confirmed the efficacy and safety of emicizumab in AHA patients. Based on 12 AHA patients undergoing first-line treatment, Knoebl and colleagues successfully applied emicizumab in combination with reduced-intensity immunosuppression. The treatment was well tolerated, and no systemic undesirable effects were reported. One patient exhibited a minor stroke while receiving repeated rhFVIIa injections, but he recovered quickly without any sequelae.[11] Chen and colleagues presented a case series at the last 2020 ASH Annual Meeting, demonstrating that the rituximab and emicizumab combination is an effective treatment for AHA, and largely devoid of undesirable effects, as based on their experience involving eight patients. After first emicizumab dose, no further haemostatic treatments or red blood cell transfusions were required except for one patient with recurrent haematuria related to a local bladder condition. At a median 102-day follow-up, no patient had experienced any haemorrhagic or thrombotic complications[12] (Table 2).

These different publications thus suggest emicizumab to be a promising therapy for this condition, which is challenging to manage. Indeed, the AHA-affected population mostly comprises elderly patients with highly prevalent comorbidities.[1,13,14] Thus, several considerations must be addressed concerning the treatment of this pathology. First, these patients present a high-risk profile for thrombotic complications linked to their haemostatic treatment and multiple other factors, such as age, cardiovascular risk factors, hospitalization, bed rest and several others. According to the experience with 23 patients published in the literature and our own two patients, no major thrombotic complications have occurred so far, apart from a minor stroke under bitherapy combining emicizumab and rhFVIIa. Second, a major limitation of bypassing agents is the lack of a validated prophylaxis strategy for patients with AHA. There is therefore a risk of recurrent severe bleeding until the inhibitor is eradicated. This explains the need for aggressive immunosuppressive therapy.[17,18] Based on the available data and our own experience, emicizumab's major advantages include its ease of use, rapid haemostatic prophylactic efficacy and reduced requirement of aggressive immunosuppressant

agents. This last advantage should not be overlooked, as infectious complications related to immunosuppression are the primary death cause in AHA patients. Up to 16% of fatal, immunosuppression-related complications were reported in the largest studies published to date.[1,3,13,14] Finally, in our experience and as reported in the literature, transfusion requirements have decreased rapidly from the first emicizumab dose onwards, thereby reducing the risk of ischaemic anaemia-related complications, as well as that of repeated transfusions, including alloimmunization, volume overload, pulmonary oedema and iron overload.[18]

From a pharmacoeconomic point of view, emicizumab displays the following advantages: single haemostatic agent at a standard weight-dependent dose, reduction in the repeated use of other FVIII-bypassing agents, reduction in transfusion requirements, reduction in hospital stay length and possibility of delaying and adapting immunosuppression with a resultant reduction in the costs of managing immunosuppression-related complications.

However, it should be emphasized that emicizumab remains a prophylactic haemostatic treatment, which cannot be used alone in patients with severe or active acute haemorrhages. In this case, using a bypassing agent (rhFVIIa) or pFVIII is absolutely indispensable. Emicizumab could then be started once the patient is haemodynamically stable. The combination of aPCC and emicizumab has been associated with a significant thrombotic risk and should be avoided.[5,18]

Under emicizumab, biological monitoring requires a specialized laboratory with appropriate assays and reagents. The management of these patients should ideally be limited to tertiary centres with expertise in using emicizumab. Monitoring the inhibitor titre and the endogenous FVIII with a chromogenic assay using bovine reagents is indeed necessary for follow-up and deciding whether to stop immunosuppression and emicizumab. As the use of emicizumab in AHA is recent, no discontinuation criteria have been validated and more data are needed.

Conclusion

We herein report on the first AHA patients treated using emicizumab in Belgium. The treatment's advantages include its rapid efficacy in preventing bleeding, ease of administration, possibility of less aggressive immunosuppression previously associated with high morbidity and mortality and reduction in thrombotic complications. This approach is likewise promising in economic terms. For these reasons, emicizumab represents a therapeutic advance and attractive alternative in AHA management. Further prospective studies are needed to validate this therapeutic approach.

Conflict of interest statement

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Ethical approval and patients' consent

Our institution does not require ethical approval for publication of case reports. Patients provided consent to use their data anonymously for the purpose of scientific publication

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