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CASE STUDY

Emicizumab in two patients with acquired haemophilia A – case report

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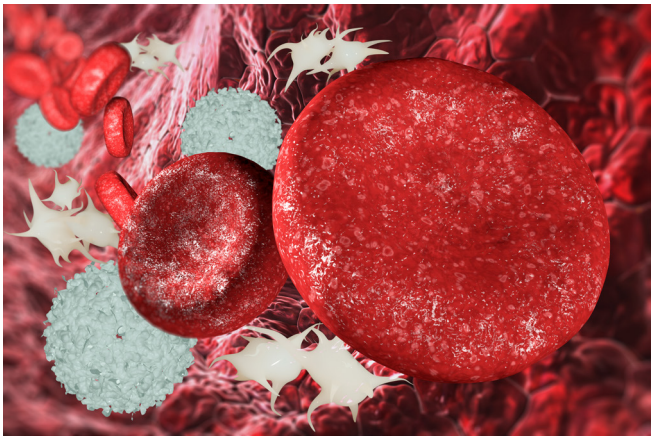

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The cases of two patients with acquired haemophilia A treated with emicizumab suggest its early initiation as part of frontline therapy may reduce episodes of bleeding and reduce the need for bypassing agents

Patients with acquired haemophilia A (PwAHA) can present with severe bleeding and may require lengthy treatment with bypassing agents and immunosuppression. We present two cases of the implementation of emicizumab in PwAHA. The first patient, an 82-year-old man with rheumatoid arthritis (RA), presented with acquired haemophilia A (AHA) and spontaneous left tibia hematoma complicated by a persistent wound and infections. After a month of intermittent bleeding at the site and immunosuppression, the inhibitor level remained elevated and he was placed on emicizumab. While on therapy, debridement of the wound required activated factor VII therapy, which was complicated by a venous thromboembolism (VTE). He was successfully managed with anticoagulation while on emicizumab until his inhibitor level was undetectable. The second patient is a 62-year-old woman, also with RA and with a persistently positive dilute Russell viper venom time who presented with intracerebral haemorrhage (ICH) and was found to have AHA. After a period of time on bypassing agents, emicizumab was started due to a persistent inhibitor level and the ICH remained stable. She only required two doses initially, however, had a relapse with recurrent factor VIII inhibitor and received three additional doses without any complications. These cases highlight that emicizumab is a viable option in the care of PwAHA in challenging scenarios such as in the context of VTE and ICH.

Keywords: *Acquired haemophilia, Emicizumab, Intracranial haemorrhage, Inhibitors, Recombinant factor VIIa, Case report*

Acquired haemophilia A (AHA) is a severe bleeding disorder caused by the development of autoantibodies to coagulation factor VIII (FVIII) [1]. AHA is often idiopathic but may be associated with malignancy, pregnancy, infection, and autoimmune disorders [1]. Management of AHA requires immunosuppression to inhibit the autoantibody and bypassing agents (BPAs) to treat bleeding complications. Steroids, rituximab and cyclophosphamide are commonly used immunosuppressive therapies (IST). BPAs, including recombinant human activated factor VIIa (rFVIIa), activated prothrombin complex concentrate (APCC), and either plasma or recombinant porcine FVIII (rpFVIII), can be effective at treating bleeds but require frequent infusions, may increase risk of thrombosis, and carry significant financial burden [2].

Emicizumab is a bispecific FVIII-mimetic monoclonal antibody that binds to activated factor IX and factor X, restoring haemostasis. It is approved for prophylaxis of bleeding in adult and paediatric patients with congenital haemophilia A (PwCHA) regardless of inhibitors [3]. Given its successful implementation in PwCHA, clinicians have explored the off-label use of emicizumab in AHA. In a case series of 12 patients with acquired haemophilia A (PwAHA) and initial FVIII activity <1%, emicizumab was administered and haemostatic efficacy was achieved within 3 days of the first dose [4]. Despite successful outcomes of emicizumab in this setting, the use of the drug is not standardised and thus uncertainty remains in its pharmacokinetics in PwAHA. Moreover, the use of emicizumab may be challenging in patients with concurrent thrombosis and/or intracerebral haemorrhage (ICH).

We report the use of emicizumab in two PwAHA with unique features: a man presenting with a left intramuscular thigh hematoma complicated by venous thromboembolism, and a woman with rheumatoid arthritis and a persistently positive lupus anticoagulant and ICH. No external funding was required for the procurement of emicizumab for these patients and the decision to use the medication was made by the consulting haematologist with agreement by the patients and their families.

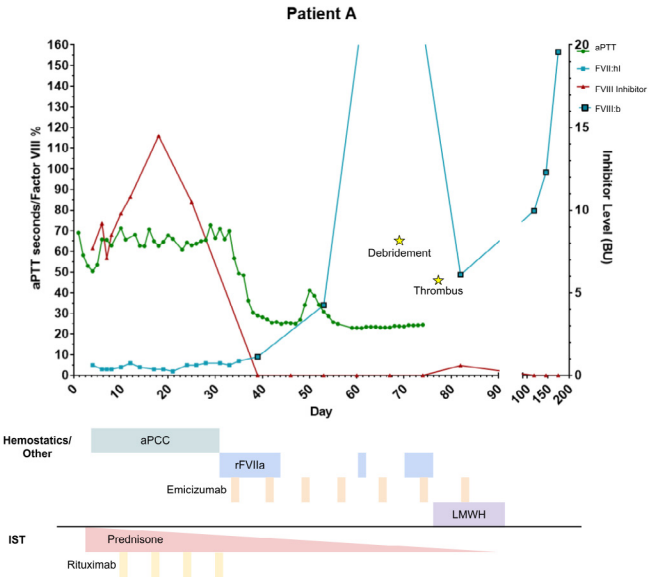
CASE REPORTS

Patient 1

An 82-year-old man with a history of rheumatoid arthritis (RA) presented to the hospital with progressive airway oedema and epiglottitis and suspected Ludwig's angina. On hospital day 2, he developed a spontaneous left tibia haematoma. His activated partial thromboplastin time (aPTT) on admission was 69.1 seconds (reference range [RR], 26.5-37.3 seconds). A mixing study showed an immediate, partial aPTT correction to 42.4 seconds. After 1-hour incubation at 37 , the aPTT prolonged to 59.4 seconds, consistent with the presence of an inhibitor against an intrinsic coagulation factor. Further evaluation revealed a FVIII activity by one-stage assay (FVIII:h) of 5%. FVIII inhibitor level was 7.7 Bethesda units (BU) (RR ≤0.5 BU), confirming the diagnosis of AHA.

The patient was initially treated with one dose of desmopressin 0.3 mcg/kg and then APCC (Figure 1). IST was initiated with prednisone 1 mg/kg daily with a prolonged taper and rituximab 375 mg/m^2 weekly for 4 weeks. During this time, the patient continued to

Figure 1. Timeline of events in care of the first patient
Days are with respect to the initial presentation. The patient's coagulation parameters and FVIII levels and inhibitor are shown in relation to administration of haemostatic agents and immunosuppressive therapy (IST) including rituximab and prednisone. On day 67 and 74, the Factor VIII levels on the one-stage assay (FVIII:h) were 273 and 278%, respectively [not shown]. Patient had debridement done on day 70 and initiated on recombinant factor VIIa (rFVIIa), subsequently developing a deep vein thrombus on day 76.



aPTT = activated partial thromboplastin time;
FVIII:b = chromogenic FVIII measurement using bovine reagent;
aPCC = activated prothrombin complex concentrate;
LMWH = low molecular weight heparin

have intermittent bleeding from a wound adjacent to the site of the haematoma on the lower leg requiring continued APCC therapy. After a month, his FVIII:h remained <10% and the decision was made to transition the patient to emicizumab. As APCC is contraindicated in patients on emicizumab due to the risk of thrombotic microangiopathies (TMA), the patient was first switched to rFVIIa (eptacog alpha) at 90 mcg/kg every 12 hours. After three days of rFVIIa, emicizumab was initiated with an overlap period of nine days at a dose of 3 mg/kg weekly for 4 doses, followed by 1.5 mg/kg weekly.

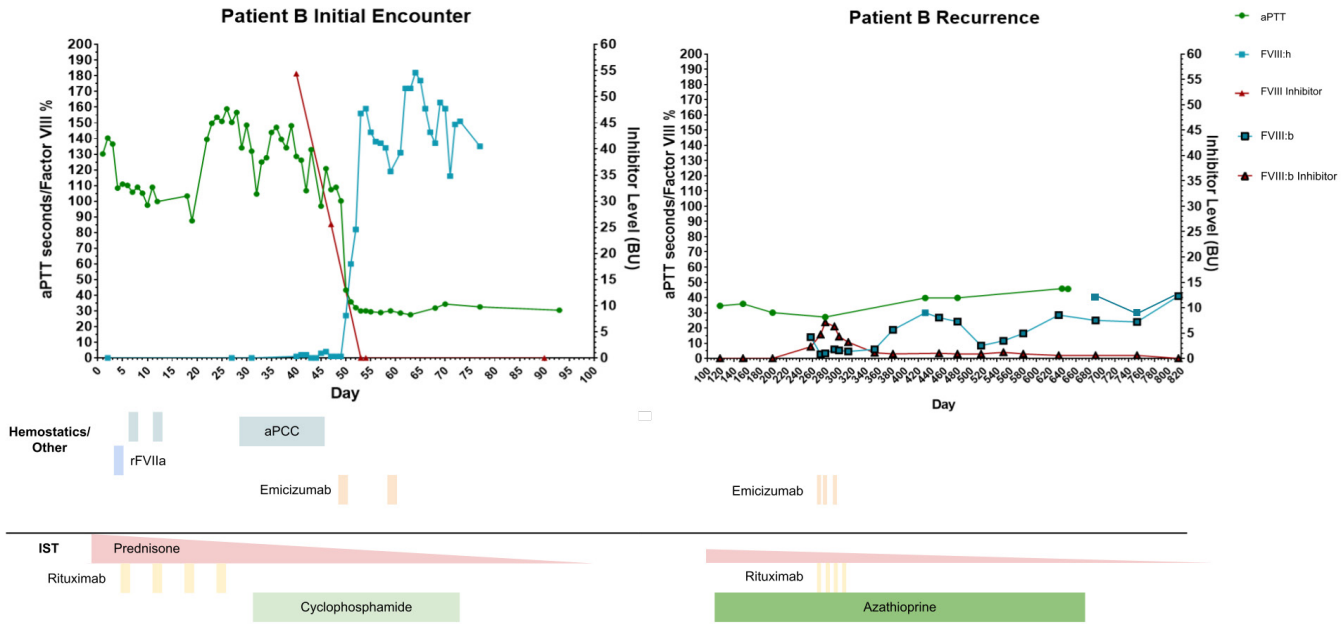
His hospital stay was complicated by septic shock in the setting of E. coli bacteremia and neutropenia and a polymicrobial left lower extremity wound infection, requiring several weeks of antibiotics and surgical debridement while the patient was on emicizumab. Recombinant FVIIa (eptacog alpha) was administered at 90 mcg/kg prior to debridement, followed by 90 mcg/kg every two hours during, and for 12 hours after the procedure. On day 4 post-debridement, rFVIIa was tapered to 90 mcg/kg every four hours for two days and then every six hours. On day 7 post-debridement, the patient was diagnosed with an occlusive right brachial vein thrombus and rFVIIa was discontinued. By this time, the aPTT had normalised and single-stage testing of FVIII inhibitor was negative. FVIII activity by chromogenic assay using bovine reagents (FVIII:b) was 35-50% with a detectable inhibitor at 0.6 chromogenic BU by chromogenic assay. Given the subnormal FVIII:b, low-dose anticoagulation was cautiously started with 20 mg of enoxaparin daily and gradually increased to 1 mg/kg daily – completing a total of three months of anticoagulation.

While on emicizumab, FVIII inhibitor level on a one-stage assay decreased to <0.5 BU 33 days after starting IST. FVIII:b activity increased to 9% shortly after starting emicizumab, to >30% 18 days after initiation. After the 3rd maintenance dose of emicizumab, FVIII:b activity was near 50% and FVIII:b inhibitor level was 0.6 chromogenic BU (76 days after starting IST). Emicizumab was discontinued. Three months post-discharge, the patient remained asymptomatic, with normal FVIII:b activity and undetectable FVIII inhibitor level.

Patient 2

A 62-year-old woman with a history of RA, persistently positive dilute Russel's viper venom time (DRVVT) and interstitial lung disease (ILD) on mycophenolate mofetil and prednisone presented to an outside hospital with bleeding from a peripherally inserted central

Figure 2. Timeline of events in care of the second patient
Days are with respect to the initial presentation. The patient's coagulation parameters and Factor VIII (FVIII) levels and inhibitor are shown in relation to administration of haemostatic agents and immunosuppressive therapy (IST) including intravenous immunoglobulin, prednisone, rituximab, and cyclophosphamide. During recurrence, the patient received 3 doses of emicizumab. Inhibitor level became undetectable three months post relapse.



aPTT = activated partial thromboplastin time; FVIII:h = FVIII measurement via one-stage assay; FVIII:b = chromogenic FVIII measurement using bovine reagent; aPCC = activated prothrombin complex concentrate

catheter for rituximab infusions. While hospitalized, she complained of headache and was found to have an intracerebral haemorrhage (ICH) with 4 cm focus without midline shift on a computed tomography (CT) head scan. Coagulation testing revealed an aPTT of 143 seconds. A mixing study showed an immediate, partial aPTT correction to 50.2 seconds and prolongation to 89.3 seconds after 1-hour incubation. FVIII:h activity was <1% and the FVIII inhibitor level was 100.0 BU, consistent with a diagnosis of AHA.

At the outside hospital, at the discretion of the local haematologist, she received rFVIIa (eptacog alpha) for two days with APCC used intermittently thereafter (Figure 2). Serial head imaging showed worsening ICH and she was started on scheduled APCC dosing. IST with increased prednisone dosing from the patient's chronic therapy, intravenous immunoglobulin (IVIG) 1 g/kg for 2 days, rituximab 375 mg/m2 weekly for 4 doses, and cyclophosphamide were administered. Cyclophosphamide therapy was complicated by severe neutropenia and discontinued. The patient was transferred to our hospital where a follow up CT head scan showed stable ICH. APCC was discontinued and emicizumab was initiated four days afterwards. The FVIII inhibitor level was decreasing, and the patient received two doses of emicizumab 210 mg before it was discontinued due to normalization of aPTT and undetectable FVIII inhibitor level using one-stage assays.

Eight months later, the patient developed new subcutaneous haematomas. FVIII:b activity was 14% and FVIII inhibitor level was 2.3 BU. At that time, she was on prednisone 25 mg daily and azathioprine 150 mg daily for her underlying RA. Emicizumab was restarted at 3 mg/kg weekly for 2 doses, followed by 1.5 mg/kg for one dose. Rituximab was administered at 375 mg/m^2 weekly for 4 doses. The inhibitor level decreased to 0.6 BU and the patient's ecchymoses resolved. Both the FVIII:h activity and the FVIII:b increased (30% and 28%, respectively) but did not normalize. Despite only receiving the three doses of emicizumab at this recurrence, the drug remained detectable in her blood months after the last dose. Forty-six days after the last dose, the drug level was 21 mcg/dL and at 80 days it was 10 mcg/dL. By one year post, the level remained detectable at 4 mcg/dL. She continued on monthly monitoring, remaining asymptomatic from bleeding. At the last follow up, 2 years and 86 days after initial presentation, the FVIII:h was 47%, FVIII:b 41% with undetectable inhibitor levels. She continues prednisone 15 mg daily and 3 litres of oxygen by nasal cannula for underlying RA and ILD and has remained free from any further haemorrhagic complication and has undergone invasive procedures without complications.

DISCUSSION

AHA is associated with severe bleeding and occurs predominantly in older adults without prior bleeding history. While the median age at diagnosis is 74 years, it can affect children and adults of all ages with an estimated prevalence of 1.5 cases per million per year [1]. Patients typically present with spontaneous or post-surgical haemorrhage, ranging in severity from mild to life-threatening. Subcutaneous bleeds are most common, followed by intramuscular, gastrointestinal, genitourinary, and retroperitoneal bleeds [5]. Diagnosis of AHA is based on its clinical picture and confirmed by a prolonged aPTT without significant correction with immediate mixing studies and further aPTT prolongation after 1-hour incubation. Further testing requires measurement of FVIII activity and Nijmegen-modified Bethesda or enzyme-linked immunosorbent assays to quantify the FVIII inhibitor level.

Treatment goals require eradication of the FVIII inhibitor with IST and the use of a BPA or rpFVIII to control bleeding. In patients with a low inhibitor titre with non-major bleeding, as in the case of the first patient, desmopressin is an option with up to 75% haemostatic efficacy [5,6]. Its use, however, is limited by tachyphylaxis and need for electrolyte monitoring, particularly in a patient with advanced age. As such, BPAs remain the first line treatment. BPAs are highly effective but have several disadvantages including the need for frequent intravenous infusions, risk of thromboembolism, development of anti-drug antibodies (ADAs), no established laboratory tests to monitor efficacy, and cost [2,7]. Although rpFVIII is specifically approved for the treatment and control of bleeding episodes in PwAHA, challenges with obtaining access to the drug (which may not be carried in many hospitals), need for dose titration, and case reports of ADAs have limited its widespread implementation [2]. IST with steroids, given as monotherapy or in combination with either cyclophosphamide and/or rituximab, is recommended for all eligible patients. However, intensity and timing of IST should be individualised due to high immunosuppression-related mortality, especially in elderly patients who tend to have multiple comorbidities and decreased performance status [8]. While IST may be effective in achieving a complete response, the relapse rate remains relatively high (as high as 25% with a median time to relapse of 14.7 weeks) [5], and this was reflected with the second

patient who relapsed at around 32 weeks after initial presentation.

Management of AHA is frequently extrapolated from that of PwCHA with inhibitors. In November 2017, emicizumab was approved for PwCHA based on data from the HAVEN trials [9-12]. Emicizumab prophylaxis significantly reduced the annualized bleeding rate compared with no prophylaxis among PwCHA with inhibitors who previously received episodic BPA treatment or who were previously on BPA prophylaxis [9,10,12]. Because of its superior efficacy, favourable safety profile, subcutaneous administration, weekly dosing, and feasible use as an outpatient therapy, emicizumab has transformed the landscape of management of PwCHA with and without inhibitors [7]. Some special considerations involving laboratory monitoring include using chromogenic FVIII assays with bovine reagents (FVIII:b) instead of aPTT and one-stage FVIII assays (FVIII:h) to monitor response due to emicizumab's interference with intrinsic, clotting-based assays [3]. Additionally, APCC should be discontinued at least 24 hours prior to initiation and avoided while receiving emicizumab due to the increased risk of TMA and thromboembolic events. Recombinant FVIIa is preferred if BPAs are required for breakthrough bleeds in persons with an inhibitor [13].

Current guidelines state emicizumab should not be used in PwAHA outside of clinical trials; however, data from ex vivo studies, case reports, and a prospective, Phase III (AGEHA) trial suggest emicizumab may be beneficial in this population [4,14-16]. Most reports describe the utility of emicizumab prophylaxis in PwAHA initially treated with BPAs and IST for subcutaneous and intramuscular haematomas [17-24], while a smaller number illustrates the risk-benefit profile of emicizumab given as either a first-line or second-line haemostatic agent [4,24-29]. In our cases presented, the haematology consult service opted to offer emicizumab therapy to the first patient due to a persistently low FVIII:h after more than a month. The experience with the first patient prompted the service to again offer emicizumab to the second patient upon transfer to this institution given their difficult course and complications with IST in the preceding hospital. Furthermore, the presence of a persistently positive DRVVT created concern for possible hypercoagulability and therefore hesitance to rely on activated factor concentrates.

In the Knoebl et al. case series, emicizumab was used as a first-line haemostatic agent along with BPAs in 12 adults PwAHA [4]. Three patients were initially treated with APCC and switched to rFVIIa due to insufficient response or adverse effects; seven patients were started on rFVIIa upfront. Initial haemostatic therapy was started a median of one day after bleeding onset. Patients received 2-3 doses of emicizumab 3 mg/kg once weekly, with the first dose being administered after a median of three days of BPA treatment. When FVIII:h exceeded 10%, the dose was reduced to 1.5 mg/kg every three weeks; emicizumab was discontinued if FVIII:h rose above 30%. A median of five doses were given. For IST, 10 patients received prednisone 1 mg/kg daily for one week, followed by taper over two weeks; all received rituximab. The median time to bleeding cessation was three days after emicizumab initiation, allowing for BPA discontinuation after a median of one and a half days, without new or breakthrough bleeds observed after the first dose of emicizumab. Factor VIII:b ≥50% was achieved after a median of 115 days.

In our two patients, BPAs were started within one day of bleeding; however, the first emicizumab dose was not administered until the first and second patient had received 31 days and 46 days of BPA treatment, respectively. The first and second patient received a total of seven and two doses of emicizumab, respectively and the second patient received 3 doses with her first relapse. Both received steroids and rituximab; however, their steroid courses were more prolonged compared to the Knoebl study. The second patient also received IVIG and cyclophosphamide. Earlier initiation of emicizumab may have allowed shorter BPA treatment durations and reduced the need for intensive IST. Neither patient experienced further bleeds after emicizumab initiation. In the first patient, FVIII:b normalised after 76 days of IST, which was faster than reported in the Knoebl et al. case series. In the second patient during recurrence, the FVIII:b remained subnormal with a low detectable inhibitor. Even though emicizumab was not continued indefinitely, the drug remained detectable in the blood months after the last dose and may have been responsible for protection despite the detectable inhibitor. This phenomenon has not previously been reported in the literature.

Regarding safety, paradoxical cases of deep venous thrombosis (DVT), both spontaneous and with associated conditions, have been described in PwAHA. In the Knoebl et al. case series, one patient experienced a minor stroke with concomitant, repetitive rFVIIa doses prior to change of a vacuum-assisted closure suction system for an infected large abdominal wound. Similarly, our first patient developed

an occlusive right brachial vein thrombus after being treated prophylactically with rFVIIa before, during, and following surgical debridement and with significantly elevated FVIII:h levels. Given the low inhibitor titre at this point in the patient's course, it is possible that FVIII rather than rFVIIa could have been used [30]. While this potentially could have reduced the risk of development of thrombosis, the inability to obtain timely FVIII:b levels complicated the ability to offer this regimen. Our patient was safely managed with anticoagulation while on emicizumab. At the healthcare provider's discretion, enoxaparin was initially administered at a low dose to ensure tolerability prior to increasing to 1 mg/kg daily. Additional instances of non-occlusive lower extremity DVTs have been reported while on maintenance therapy with emicizumab [16,24]. These examples highlight the infrequent but serious risk of thromboembolic complications that can happen during emicizumab monotherapy and coadministration with BPAs, especially in older hospitalized patients. Optimal management of patients with thrombotic complications while on emicizumab remains challenging but these cases highlight that anticoagulation can be used safely and effectively once the FVIII has normalised and the FVIII inhibitor is eradicated. This case also underscores our limited understanding of how to manage patients on emicizumab who require surgery or procedures.

Some unique aspects of our cases include the treatment of venous thromboembolism in our first patient as detailed above and the presence of a persistently positive lupus anticoagulant in our second patient without any thrombotic complications. Furthermore, in the second case, the patient presented with ICH and managed safely with emicizumab. When combining available literature and real-world experiences, it is reasonable to support the use of emicizumab treatment in PwAHA. Emicizumab appears to be beneficial in reducing bleeding complications and shortening the length of BPA use. At present, there is no consensus regarding the optimal dosing strategy and discontinuation criteria that should be followed for emicizumab prophylaxis or treatment. Our case demonstrates that long after discontinuation, the drug may remain detectable in the blood. Early initiation as part of frontline therapy may reduce episodes of bleeding and reduce the need for BPAs and their associated costs and complications. The data at present support this notion and further collaborative studies or global registries are warranted to investigate its use as a frontline therapy for PwAHA.

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Informed consent has been obtained from the individuals reported in this case study.

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