Ther Adv Hematol
2021, Vol. 12: 1–6
DOI: 10.1177/20406207211040345

Challenges of biological monitoring in a hemophilia A patient without inhibitors on emicizumab undergoing major orthopedic surgery: a case report

Louise Guillaume, Marie-Astrid van Dievoet, Catherine Lambert and Cedric Hermans

***Abstract*:** A man with severe hemophilia A (HA) without factor VIII (FVIII) inhibitors was admitted for total arthroplasty of his elbow. The patient was being treated with emicizumab, with his last administration given 8 days before surgery. Preoperatively, he received a bolus of 4000 international units (IU) of recombinant (r)FVIII. Throughout the operation, a continuous infusion of 4 IU/kg/h was administered and maintained over 24 hours. On the first postoperative day, the FVIII infusion rate was reduced to 225 IU/h for 4 days and stopped on the fifth day. Under this treatment, no bleeding complications occurred. Emicizumab is known to interfere with a wide range of coagulation assays, thereby challenging replacement therapy monitoring before, during, and after surgery. In this case study, we report on the assessment of FVIII levels at different time points using various reagents. We conclude that for both hematologists and non-hematology clinicians, it is crucial to be aware of emicizumab interferences with routine coagulation tests so as to avoid misinterpretation. In addition, laboratory specialists must be familiar with this treatment in order to select appropriate coagulation tests and provide rapid and reliable result interpretations.

Keywords: APTT, case report, emicizumab, hemophilia, major surgery

Received: 16 June 2021; revised manuscript accepted: 23 July 2021.

Correspondence to:
Louise Guillaume
Department of Laboratory, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain (UCLouvain), Brussels, Belgium.
louise.guillaume@uclouvain.be

Marie-Astrid van Dievoet
Department of Laboratory, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain (UCLouvain), Brussels, Belgium

Catherine Lambert
Cedric Hermans
Haemostasis and Thrombosis Unit/ Haemophilia Treatment Centre/Division of Haematology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain (UCLouvain), Brussels, Belgium

Background

Hemophilia A is an X-linked genetic disorder characterized by a deficiency in clotting factor (F) VIII. The main symptom in affected patients is their bleeding tendency that primarily involves the musculoskeletal system.[1] Based on FVIII activity, three different forms of hemophilia are distinguished: mild (5-40 IU/dL FVIII), moderate (1-5 IU/dL FVIII), and severe (<1 IU/dL FVIII) hemophilia. Until recently, the mainstay treatment for severe hemophilia A (SHA) was prophylaxis with exogenous FVIII administered intravenously. Nevertheless, due to the short half-life of currently available FVIII concentrates, at least two injections per week were required to maintain minimum protection levels.[2] Moreover, in up to 30% of patients, FVIII alloantibodies, also called inhibitors, can develop over time.[3]

Emicizumab (Hemlibra®; F. Hoffmann-La Roche, Basel, Switzerland) represents an alternative prophylactic treatment option for SHA patients.[4] Being a humanized bispecific antibody, it binds to activated FIX (FIXa) and FX, thereby mimicking the function of FVIIIa in restoring hemostasis.[5] Excellent results were seen in the HAVEN trials [6] for HA patients, both with and without inhibitors. In March 2020, emicizumab received reimbursement approval in Belgium for HA patients of all age groups with FVIII inhibitors, As well as for SHA patients without inhibitors.[7]

Recent studies have shown that this drug causes numerous challenges with respect to the coagulation tests required for assessing and monitoring FVIII deficiency, and for administrating replacement therapy at times of invasive procedures. Emicizumab affects the laboratory assays by shortening the activated partial thromboplastin time (aPTT) that is employed to diagnose hemophilia and monitor replacement therapy with exogenous FVIII. The one-stage assay (OSA), which is routinely applied to measure FVIII activity as based on the aPTT, can therefore no longer be employed. The FVIII chromogenic substrate assay (CSA) represents a valid alternative. Nonetheless, emicizumab causes interferences that are reagent-specific. If the chromogenic assay employs human reagents, the humanized antibody is able to recognize FIXa and FX present in the kit, with a FVIII-like activity measured. No interference is, however, seen when using CSA with bovine reagents, given that the antibody does not recognize coagulation factors of animal origin.[4] When employing CSA with hybrid reagents (human FIXa and bovine FX), emicizumab can theoretically interfere with the test at very high concentrations.[5]

We herein report the biological monitoring by means of different assays in a SHA patient who, while being treated with emicizumab, underwent major orthopedic surgery under continuous FVIII infusion.

Case presentation

A 44-year-old man with SHA, secondary to intron 22 inversion of the FVIII gene, was admitted for total arthroplasty of his right elbow. His medical history was remarkable for a chronic hepatitis C virus infection that was cured in 2017. Previously, he had undergone a synoviothesis of the right elbow and total joint replacement of the right knee under continuous infusion with standard half-life (SHL) FVIII. Emicizumab (6 mg/kg every 4 weeks) treatment was initiated in July 2020, which was justified by a high annualized spontaneous bleeding rate despite SHL FVIII prophylaxis given three times a week, an increasingly problematic vascular access, and progressive joint deterioration with functional and occupational repercussions.

The last emicizumab administration had been given 8 days prior to the operation. No FVIII inhibitors were demonstrated pre-operatively by either the Nijmegen-Bethesda reference method or enzyme-linked immunosorbent assay (ELISA) method. The residual FVIII activity in the Nijmegen-Bethesda assay was analyzed using a bovine chromogenic assay (Chromogenix Coamatic® FVIII; Diapharma, West Chester, USA). The patient received a bolus of 4000 IU of rFVIII (ReFacto AF®; Pfizer, New York, USA) preoperatively. Throughout the operation, a continuous infusion of 4 IU/Kg/hour was administered,[8,9]that is, 280 IU/h and maintained for 24 hours. On the first post-operative day, the FVIII infusion rate was reduced to 225 IU/h for 4 days and then stopped on Day 5. Under this treatment, no hemorrhagic complications were documented.

Outcome and follow-up

Plasma FVIII levels were measured at five different time points before and after surgery with three assays (Table 1) using the OSA (HemosIL® SynthASIL; Werfen, Barcelona, Spain), human (BIOPHEN FVIII:C; HYPHEN BioMed, Neuville-sur-Oise, France), and bovine chromogenic assays (Chromogenix Coamatic® FVIII).

Discussion

We have herein reported the management and biological monitoring of a SHA patient on emicizumab without inhibitors who underwent major orthopedic surgery (Table 1). The FVIII OSA revealed a concentration $>$ 200 IU/dL due to emicizumab interference. This assay is the default test used, and thus misinterpretation would lead to erroneous clinical decisions. In this specific case, the surgeon could have started the operation solely based on the OSA information. Further information pertaining to this patient's treatment was crucial in selecting the right test.

Differences between the CSA using human versus bovine reagents were minor at high FVIII concentrations, notably immediately post-bolus and postoperatively on Days 0 to 4. This is probably explained by emicizumab displacement at these high concentrations. As expected, differences were significant before the FVIII bolus due to emicizumab interference in the CSA using human reagents.

As previously discussed, emicizumab is a bispecific monoclonal antibody[10] that interferes with the aPTT assay by binding to both human FIXa

Table 1. Results of FVIII assays in the perioperative period using different laboratory assays.

	OSA (IU/dL)	Bovine chromogenic factor VIII assay (IU/dL)	Human chromogenic factor VIII assay (IU/dL)
Pre-bolus FVIII	>200	< 1	10
Post-bolus FVIII	>200	137	121
POD 0	/	121	102
POD 1	/	143	140
POD 5	/	137	146

FVIII, factor VIII; OSA, one-stage-assay; POD, postoperative day.

and FX. In contrast to FVIII, as emicizumab does not require activation by thrombin, it is immediately effective.[4] The aPTT is, therefore, most likely shortened, resulting in higher-than normal FVIII levels.[1] Given that this molecule's elimination half-life is 30 days, the complete disappearance of this interference can theoretically only be obtained after more or less 5 months (ie, five half-life times).[10] Interferences caused by emicizumab must be carefully considered in order to correctly monitor FVIII levels.[11] It is crucial for both hematologists and non-hematologist clinicians to be aware of this interference in order to avoid misinterpretations. In parallel, laboratory specialists must similarly be familiar with this treatment in order to select the appropriate coagulation assays and provide a quick and reliable interpretation of the results.

The World Federation of Hemophilia recommends using the bovine chromogenic method to determine endogenous FVIII levels in patients on emicizumab.[1] The French Study Group on the Biology of Hemorrhagic Diseases (BIMHO) recommends employing appropriate biological tests to monitor the hemostasis of patients being treated with emicizumab according to various clinical situations. In the absence of bleeding or surgery, specific monitoring is not necessary. However, during surgery and bleeding, the choice of the tests likely depends on the treatment used. If FVIII concentrates are added to a patient on emicizumab, the CSA using animal-origin reagents is mandatory.[4] Today, the easiest and most presumptive method for measuring emicizumab plasma concentrations is a modified version of the aPTT-based FVIII OSA (r2 Diagnostics, South Bend, Indiana, United States). The only difference from the original test is the higher patient sample dilution, as well as the use of emicizumab-containing calibrators.[12,13]

Emicizumab prophylaxis during surgical procedures reduces the bleeding tendency, yet without abolishing it completely. Depending on the type of surgery, different recommendations exist for patients without inhibitors that are receiving such treatment. For minor surgery procedures including central venous catheter insertion, endoscopy with biopsy, or dental/oral procedures, pre-operative FVIII concentrates are not necessarily required. For invasive procedures with a major bleeding risk like gastrointestinal endoscopic surgery, or for major surgery, a preprocedural FVIII injection should be administered. The recommended dose, which is associated with bleeding risks, is dependent on the operation type, that is, 40 to 50 IU/kg of FVIII for major surgery.[1,11,14]

The combination of emicizumab and FVIII may lead to an additive hemostatic activity. Ferrière and colleagues studied this interaction in a FVIII-deficient mouse model. When either a single FVIII dose (5 U/kg) or emicizumab (3 mg/kg) was administered, the bleeding was not completely corrected. However, when a combination of both was given, the blood loss was controlled in line with what was observed after administering a higher FVIII dose alone (7.5 U/kg).[15] Based on these findings, we can hypothesize that, if a low FVIII dose is administered to an emicizumab-treated patient, both molecules are able to find sufficient substrates, with hemostasis being restored by this combination. However, when an

excessive dose is given, emicizumab and FVIII will enter into competition. Since FVIII's affinity for the specific binding sites of FIXa and FX is approximately 10-fold higher than that of emicizumab, this drug is rapidly displaced and thrombin generation is enhanced by circulating FVIII.[11,16] According to published data, the combination of emicizumab and rFVIII is not associated with a risk of thromboembolic complications, including thrombotic microangiopathy. However, due to the relatively small number of patients treated, few bleeding episodes, and short monitoring period, this hypothesis must still be confirmed by real-world clinical data.[1,11,17]

Nakajima and colleagues[18] demonstrated in patients with mild/moderate hemophilia that emicizumab increased the ex vivo coagulation potential.

Available data regarding surgical procedures and emicizumab use have mostly been reported from patients with FVIII inhibitors. Several authors[3,19–21] described cases of HA patients with inhibitors being treated with emicizumab who underwent a major operation. In these patients, rFVIIa was combined with emicizumab before and during the operation, and in the postoperative setting, as well. Biron-Andreani and colleagues[20] reported a SHA case with a low titer inhibitor (<5BU/mL) on emicizumab who underwent total hip replacement. Plasma-derived FVIII was administered, and no thromboembolic complications were observed.

In the years to come, the number of hemophilia patients on emicizumab that require surgery is likely to increase. Therefore, it is crucial that these patients are properly managed by a multidisciplinary team. In the current guidelines, exogenous FVIII administration is recommended depending on the type of procedure. In addition, patient care must be provided in a center with a specialized hemostasis laboratory. Since emicizumab significantly shortens aPTT, FVIII OSA based on aPTT can no longer be used. Moreover, this drug is known to cause reagent-specific interference. Therefore, FVIII therapy in patients on emicizumab should be monitored with CSA using bovine reagents to avoid misinterpretation of results; in our case, however, at high FVIII concentrations, we did not observe any major differences between CSAs using either bovine or human reagents.

It must be noted that there is very little real-world data on emicizumab-treated patients without inhibitors that undergo surgical interventions. Therefore, we believe it is important to share our clinical experience.

Take home messages

- This case deals with a SHA patient without FVIII inhibitors who while being treated with emicizumab underwent major orthopedic surgery.
- The patient received a rFVIII bolus. Throughout the surgical procedure and for a further five days thereafter, a continuous FVIII infusion was administered. Under this treatment, no bleeding complications occurred.
- Plasma FVIII levels were measured at five different time points before and after surgery using different assays. Using the bovine chromogenic method avoids interferences with emicizumab.
- Effective communication among the multidisciplinary team members, including the hematologist, surgeon, and laboratory specialists, appears crucial for proper patient management and biological monitoring.

Authors' note

This case report is written according to CARE guidelines.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Ethics approval is not required for this clinical case.

Informed consent

The patient has given consent for the treatment and the writing of the case report.

ORCID iDs

Louise Guillaume https://orcid.org/0000-0002-8416-8956

Cedric Hermans https://orcid.org/0000-0001-5429-8437

Supplemental material

Supplemental material for this article is available online.

References

1. Srivastava A, Santagostino E, Dougall A, *et al*. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia* 2020; 26: 1–158. DOI: 10.1111/hae.14046.
2. Mahlangu J, Oldenburg J, Paz-Priel I, *et al*. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med* 2018; 379: 811–822. DOI: 10.1056/nejmoa1803550.
3. Seaman CD and Ragni MV. Emicizumab use in major orthopedic surgery. *Blood Adv* 2019; 3: 1722–1724. DOI: 10.1182/bloodadvances.2019000228.
4. Nougier C, Jeanpierre E, Ternisien C, *et al*. Emicizumab treatment: impact on coagulation tests and biological monitoring of haemostasis according to clinical situations (BIMHO group proposals). *Eur J Haematol* 2020; 105: 675–681. DOI: 10.1111/ejh.13490.
5. Jenkins PV, Bowyer A, Burgess C, *et al*. Laboratory coagulation tests and emicizumab treatment A United Kingdom Haemophilia Centre Doctors' Organisation guideline. *Haemophilia* 2020; 26: 151–155. DOI: 10.1111/hae.13903.
6. Pipe SW, Shima M, Lehle M, *et al*. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. *Lancet Haematol* 2019; 6: e295–e305. DOI: 10.1016/S2352-3026(19)30054-7.
7. https://ondpanon.riziv.fgov.be/SSPWebApplicationPublic/fr/Public/ProductSearch (accessed 12 November 2020).
8. Prelog T, Dolničar MB and Kitanovski L. Low-dose continuous infusion of factor VIII in patients with haemophilia A. *Blood Transfus* 2016; 14: 474–480. DOI: 10.2450/2015.0080-15.
9. Park YS, Shin WJ, Kim K, *et al*. Comparison of continuous infusion versus bolus injection of factor concentrates for blood management after total knee arthroplasty in patients with hemophilia. *BMC Musculoskelet Disord* 2017; 18: 1–5. DOI: 10.1186/s12891-017-1720-0.
10. Susen S, Gruel Y, Godier A, *et al*. Management of bleeding and invasive procedures in haemophilia A patients with inhibitor treated with emicizumab (Hemlibra®): proposals from the French network on inherited bleeding disorders (MHEMO), the French Reference Centre on Haemophilia, in collaboration with the French Working Group on Perioperative Haemostasis (GIHP). *Haemophilia* 2019; 25: 731–737. DOI: 10.1111/hae.13817.
11. Coppola A, Castaman G, Santoro RC, *et al*. Management of patients with severe haemophilia a without inhibitors on prophylaxis with emicizumab: AICE recommendations with focus on emergency in collaboration with SIBioC, SIMEU, SIMEUP, SIPMeL and SISET. *Haemophilia* 2020; 26: 937–945. DOI: 10.1111/hae.14172.
12. Lowe A, Kitchen S, Jennings I, *et al*. Effects of Emicizumab on APTT, FVIII assays and FVIII Inhibitor assays using different reagents: results of a UK NEQAS proficiency testing exercise. *Haemophilia* 2020; 26: 1087–1091. DOI: 10.1111/hae.14177.
13. Müller J, Pekrul I, Pötzsch B, *et al*. Laboratory monitoring in emicizumab-treated persons with hemophilia A. *Thromb Haemost* 2019; 119: 1384–1393. DOI: 10.1055/s-0039-1692427.
14. Fontana P, Alberio L, Albisetti M, *et al*. Management of bleeding events and invasive procedures in patients with haemophilia A without inhibitors treated with emicizumab. *Swiss Med Wkly* 2020; 150: w20422. DOI: 10.4414/smw.2020.20422.
15. Ferrière S, Peyron I, Christophe OD, *et al*. A hemophilia A mouse model for the in vivo assessment of emicizumab function. *Blood* 2020; 136: 740–748. DOI: 10.1182/blood.2019004334.
16. Bravo MI, Raventós A, Pérez A, *et al*. Non-additive effect on thrombin generation when a plasma-derived factor VIII/von Willebrand factor (FVIII/VWF) is combined with emicizumab in vitro. *J Thromb Haemost* 2020; 18: 1934–1939. DOI: 10.1111/jth.14887.
17. Makris M, Iorio A and Lenting PJ. Emicizumab and thrombosis: the story so far. *J Thromb Haemost* 2019; 17: 1269–1272. DOI: 10.1111/jth.14556.
18. Nakajima Y, Nogami K, Yada K, *et al*. Emicizumab improves ex vivo clotting function in patients with mild/moderate hemophilia A.

Thromb Haemost 2020; 120: 968–976. DOI: 10.1055/s-0040-1710315.

19. Santagostino E, Mancuso ME, Novembrino C, *et al*. Rescue factor VIII replacement to secure hemostasis in a patient with hemophilia A and inhibitors on emicizumab prophylaxis undergoing hip replacement. *Haematologica* 2019; 104: e380–e382. DOI: 10.3324/haematol.2018.215129.
20. Biron-Andreani C, Diaz-Cau I, Ranc A, *et al*. Major surgery management in patients with haemophilia A and inhibitors on emicizumab prophylaxis without global coagulation monitoring. *Br J Haematol* 2020; 189: e100–e103. DOI: 10.1111/bjh.16512.
21. Kizilocak H, Yukhtman CL, Marquez-Casas E, *et al*. Management of perioperative hemostasis in a severe hemophilia A patient with inhibitors on emicizumab using global hemostasis assays. *Ther Adv Hematol*. Epub ahead of print 27 June 2019. DOI: 10.1177/2040620719860025.