EXCEPTIONAL CASE REPORT

blood advances

# Emicizumab use in major orthopedic surgery

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**Key Points**

- Major orthopedic surgery can be performed safely in hemophilia patients with inhibitors receiving emicizumab.

## Introduction

Hemophilia A is an X-linked congenital bleeding disorder caused by a deficiency of factor VIII (FVIII) and characterized by spontaneous or traumatic bleeding into joints, muscles, and body cavities.[1] Clotting factor concentrate, recombinant FVIII (rFVIII), is necessary to treat and prevent bleeding. Unfortunately, FVIII alloantibodies (inhibitors) develop in ~30% of patients and are among the most severe and challenging complications of hemophilia.[2] Bypassing agents (BPAs), activated rFVII (rFVIIa), and activated prothrombin complex concentrate (APCC) are administered to treat and prevent bleeding in inhibitor patients; however, BPAs are not as effective as rFVIII, with 10% to 20% of bleeding events in hemophilia patients with high-titer inhibitors unable to be controlled.[3] Therefore, despite the frequent presence of advanced arthropathy resulting from repeated hemarthrosis and an associated negative impact on quality of life, there has been hesitancy to perform elective major orthopedic surgeries in such patients.[4]

More recently, emicizumab was developed to prevent bleeding in patients with hemophilia A and inhibitors.[5] Emicizumab is a humanized bispecific monoclonal antibody functionally similar to, but structurally distinct from, FVIII that binds to and bridges FIXa and FX. Its prolonged half-life of ~30 days allows for prophylactic subcutaneous administration once a week, every other week, or monthly.[6] Results from the HAVEN 1 trial in hemophilia A patients with inhibitors demonstrated an 87% reduction in annualized bleeding rate compared with no BPA prophylaxis. When compared with prior BPA prophylaxis, there was a 79% reduction in annualized bleeding rate.[7]

Although emicizumab is superior to BPAs in preventing bleeding among patients with hemophilia A and inhibitors, the unique pharmacokinetics of emicizumab do not afford precise monitoring of coagulation, which is important perioperatively.[8] Furthermore, there are limited data regarding the use of emicizumab perioperatively, especially with major surgeries. Moreover, the risk of thrombotic microangiopathy (TMA) reported with concomitant use of APCCs with emicizumab restricts its use in the surgical setting.[9]

## Case description

In this report, we describe the use of emicizumab for the first time in a 54-year-old man with moderate hemophilia A, FVIII of 0.03 IU/mL, and a high-titer inhibitor (historical peak titer, 44.8 Bethesda units [BU]), undergoing total hip arthroplasty. His comorbidities included advanced arthropathy of multiple joints, including prior total knee arthroplasty. He had a severe bleeding phenotype characterized by recurrent hemarthrosis and soft tissue bleeds. Because of the severity of bleeding, the patient received 100 IU/kg of rFVIII fusion protein daily, along with 85 IU/kg of APCC daily, alternating every other day with 90 μg/kg of rFVIIa daily. Despite this regimen, the patient continued to experience several bleeding events monthly. After emicizumab became available, it was started in this patient, and rFVIII fusion protein and BPAs were stopped. In the 12 months after beginning emicizumab therapy, the patient experienced no bleeds and reported a substantial increase in activity.

## Methods

Total hip arthroplasty was arranged to coincide with the patient's regularly scheduled emicizumab maintenance dose of 1.5 mg/kg, which was administered the morning of the surgery (Table 1). The patient received 180 μg/kg of rFVIIa immediately before the surgery. Afterward, 90 μg/kg of rFVIIa was

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**Table 1. Hip arthroplasty perioperative hemostasis regimen with emicizumab**

| Time | Single dose | Interval, h | | | |
|---|---|---|---|---|---|
| | | 3 | 6 | 8 | 12 |
| Preoperative | Emicizumab 1.5 mg/kg | | | | |
| Preoperative | rFVIIa 180 μg/kg | | | | |
| POD 0 | | rFVIIa 90 μg/kg | | | |
| POD 1 | | rFVIIa 90 μg/kg | | | |
| POD 2 | | rFVIIa 90 μg/kg | | | |
| POD 3 | | rFVIIa 90 μg/kg | | | |
| POD 4 | | | rFVIIa 90 μg/kg | | |
| POD 5 | | | rFVIIa 90 μg/kg | | |
| POD 6 | | | rFVIIa 90 μg/kg | | |
| POD 7 | Emicizumab 1.5 mg/kg | | rFVIIa 90 μg/kg | | |
| POD 8 | | | | rFVIIa 90 μg/kg | |
| POD 9 | | | | rFVIIa 90 μg/kg | |
| POD 10 | | | | rFVIIa 90 μg/kg | |
| POD 11 | | | | rFVIIa 90 μg/kg | |
| POD 12 | | | | | rFVIIa 90 μg/kg |
| POD 13 | | | | | rFVIIa 90 μg/kg |
| POD 14 | Emicizumab 1.5 mg/kg | | | | rFVIIa 90 μg/kg |

POD, postoperative day.

administered every 3 hours. The frequency of administration was changed to every 6 hours on POD 4. Subsequently, dosing was decreased to every 8 hours on POD 8. On POD 12, rFVIIa was administered every 12 hours until it was stopped on POD 14. This tapering schedule was established, in part, based on the patient's bleeding history and previous perioperative BPA use. No additional rFVIIa was administered. Because of the association with TMA, no APCC was administered. No laboratory monitoring for TMA was performed. Emicizumab was continued weekly as regularly scheduled. By contrast, the patient's previous left knee arthrotomy, synovectomy, and excisional debridement of soft tissue to bone without emicizumab required intensive therapy alternating rFVIIa and APCC, tapered over a period of 8 weeks to maintain hemostasis (Table 2).

Emicizumab and rFVIIa were effective in maintaining hemostasis without adverse events. There was an estimated blood loss of 500 mL intraoperatively (mean ± standard deviation intraoperative

**Table 2. Knee arthrotomy, synovectomy, and excisional debridement of soft tissue to bone perioperative hemostasis regimen without emicizumab**

| Time | Single dose | Interval, h | | | |
|---|---|---|---|---|---|
| | | 3* | 4 | 6 | 12 |
| Preoperative | rFVIIa 180 μg/kg | | | | |
| POD 0-13 | | rFVIIa 90 μg/kg and APCC 5000 IU | | | |
| Preoperative (CVC placement on POD 14)† | rFVIIa 180 μg/kg | | | | |
| POD 0-13 | | rFVIIa 90 μg/kg and APCC 5000 IU | | | |
| POD 14-27 | | | rFVIIa 90 μg/kg and APCC 5000 IU | | |
| POD 28-41 | | | | rFVIIa 90 μg/kg and APCC 5000 IU | |
| POD 42-55‡ | | | | | rFVIIa 90 μg/kg and APCC 5000 IU |

CVC, central venous catheter.
*Interval describes duration between alternating rFVIIa and APCC therapy (ie, rFVIIa alternating with APCC every 3 hours).
†On POD 14, CVC placement was necessary, so tapering regimen was restarted.
‡After POD 55, regular bypassing agent prophylaxis regimen was resumed.

blood loss in nonhemophilia patient, 220 ± 115.6 mL).[10] There was no evidence of hemarthrosis or soft tissue hematoma postoperatively. Hemoglobin decreased from 12.9 to 11.8 g/dL on POD 1 and then remained stable. No blood transfusions were necessary. There was no evidence of thrombosis. No other adverse events were experienced. The patient was discharged on POD 4.

## Results and discussion

To our knowledge, our case report is the first to describe the successful use of emicizumab in a patient with hemophilia A and an inhibitor undergoing joint replacement. Data regarding the use of emicizumab in major orthopedic surgery are limited. Kruse-Jarres et al[11] described a case of knee arthroscopy with synovectomy, debridement of arthrofibrosis, and chondroplasty in a 12-year-old inhibitor patient. He received 11 doses (total dose, 1016 μg/kg) of rFVIIa the day of the surgery and on POD 1. Postoperative bleeding did occur, requiring an additional 40 doses (total dose, 3326 μg/kg) of rFVIIa over the next 15 days. Santagostino et al[12] described a case of total hip arthroplasty in a 56-year-old man with hemophilia A and an inhibitor. The patient received 100 μg/kg of rFVIIa preoperatively. Intraoperative blood loss was reported as 650 mL. Postoperatively, the patient received 80 μg/kg of rFVIIa every 3 hours. On POD 1, the patient developed a hematoma of the thigh, and his hemoglobin decreased from 12.7 to 6.6 g/dL, requiring transfusion of several units of red blood cells. Subsequently, rFVIIa was changed to plasma-derived FVIII, given a low-titer inhibitor of 2 BU, which was administered as a continuous infusion until POD 8. At that time, the inhibitor titer had increased to 24 BU, so plasma-derived FVIII was switched back to rFVIIa at 80 μg/kg every 4 to 8 hours, along with antifibrinolytics, until POD 13. Ziwoski et al[13] reported a case of a 45-year-old inhibitor patient undergoing elbow synovectomy with radial head excision who received 90 μg/kg of rFVIIa preoperatively. No rFVIIa was administered postoperatively. No abnormal bleeding occurred.

According to our experience, major orthopedic surgery in patients with hemophilia A and inhibitors receiving emicizumab requires rFVIIa for adequate perioperative hemostasis; however, dose, frequency, and duration of therapy are unclear (eg, tapering rVIIa over a period of several days, rather than 2 weeks, may have been sufficient to prevent postoperative bleeding in our patient). In conclusion, this case report is novel in demonstrating that joint replacement can be performed safely in patients with hemophilia A and an inhibitor receiving emicizumab. Furthermore, it provides hematologists with guidance on the perioperative management of similar patients. This is essential as inhibitor patients with advanced arthropathy requiring orthopedic surgery transition to emicizumab. Its use may allow for successful surgeries not previously thought possible because of fear of inadequate hemostasis.

## Authorship

Contribution: C.D.S. and M.V.R. designed and completed the research, analyzed the data, formulated the conclusions, and wrote the paper.

Conflict-of-interest disclosure: C.D.S. has served on advisory boards from Bayer, Genentech, and Spark Therapeutics. M.V.R. has received research funding from Alnylam, Biomarin, Bioverative, Opko, Sangamo, Takeda, and Spark Therapeutics and served on advisory boards from Alnylam, Bayer, Biomarin, Bioverative, MOGAM, Takeda, and Spark Therapeutics.

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