

# 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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup>

More recently, emicizumab was developed to prevent bleeding in patients with hemophilia A and inhibitors.<sup>5</sup> 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.<sup>6</sup> 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.<sup>7</sup>

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.<sup>8</sup> 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.<sup>9</sup>

## 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

**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,  $220 \pm 115.6$  mL).<sup>10</sup> 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<sup>11</sup> 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  $\mu$ g/kg) of rFVIIa the day of the surgery and on POD 1. Postoperative bleeding did occur, requiring an additional 40 doses (total dose, 3326  $\mu$ g/kg) of rFVIIa over the next 15 days. Santagostino et al<sup>12</sup> described a case of total hip arthroplasty in a 56-year-old man with hemophilia A and an inhibitor. The patient received 100  $\mu$ g/kg of rFVIIa preoperatively. Intraoperative blood loss was reported as 650 mL. Postoperatively, the patient received 80  $\mu$ g/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  $\mu$ g/kg every 4 to 8 hours, along with antifibrinolytics, until POD 13. Ziowski et al<sup>13</sup> reported a case of a 45-year-old inhibitor patient undergoing elbow synovectomy with radial head excision who received

90  $\mu$ g/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 rFVIIa 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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## References

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al; Treatment Guidelines Working Group on behalf of the World Federation of Hemophilia. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1):e1-e47.
2. Gouw SC, van den Berg HM, Fischer K, et al; PedNet and Research of Determinants of INhIBitor development (RODIN) Study Group. Intensity of factor VIII treatment and inhibitor development in children with severe hemophilia A: the RODIN study. *Blood*. 2013;121(20):4046-4055.
3. Teital J, Berntorp E, Collins P, et al. A systematic approach to controlling problem bleeds in patients with severe congenital hemophilia A and high-titer inhibitors. *Haemophilia*. 2007;13(3):256-263.
4. Scalone L, Mantovani LG, Mannucci PM, Gringeri A; COCIS Study investigators. Quality of life is associated to the orthopaedic status in haemophilic patients with inhibitors. *Haemophilia*. 2006;12(2):154-162.
5. Weyand AC, Pipe SW. New therapies for hemophilia. *Blood*. 2019;133(5):389-398.
6. Callaghan MU, Sidonio R, Pipe SW. Novel therapeutics for hemophilia and other bleeding disorders. *Blood*. 2018;132(1):23-30.
7. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017;377(9):809-818.
8. Genentech. Hemlibra package insert. [https://www.gene.com/download/pdf/hemlibra\\_prescribing.pdf](https://www.gene.com/download/pdf/hemlibra_prescribing.pdf). Accessed 3 March 2019.
9. Young G. Implementing emicizumab in hemophilia inhibitor management: emicizumab should be prescribed after tolerance. *Blood Adv*. 2018;2(20):2780-2782.
10. Prasad N, Padmanabhan V, Mullaji A. Blood loss in total knee arthroplasty: an analysis of risk factors. *Int Orthop*. 2007;31(1):39-44.
11. Kruse-Jarres R, Callaghan M, Croteau S, et al Surgical experience in two multicenter, open-label phase 3 studies of emicizumab in persons with hemophilia A with inhibitors (HAVEN 1 and HAVEN 2) [abstract]. *Blood*. 2017;130(suppl 1). Abstract 89.
12. Santagostino E, Mancuso M, Novembrino C, et al Management of joint replacement in hemophilia A with inhibitors during emicizumab prophylaxis [abstract]. *Blood*. 2017;130(suppl 1). Abstract 2360.
13. Ziowski K, Batsuli G, Reding M, et al Maintaining perioperative hemostasis in patients with severe hemophilia A and inhibitors receiving emicizumab prophylaxis [abstract]. *Blood*. 2018;132(suppl 1). Abstract 635.