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REVIEW ARTICLE

Concomitant use of bypassing agents with emicizumab for people with haemophilia A and inhibitors undergoing surgery

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Abstract

Introduction: Surgery in people with haemophilia and factor VIII inhibitors is typically managed with perioperative administration of haemostatic agents to prevent or control the occurrence of bleeding events. Practical experience of surgery in patients with inhibitors who are receiving treatment with emicizumab is growing; however, the novelty of the situation means that standardised guidelines are lacking with regard to the concomitant administration of haemostatic agents, including dose and laboratory monitoring.

Aim: To review approaches to haemostatic management during major and minor invasive procedures in patients with haemophilia A and inhibitors, and to provide recommendations for controlling bleeding events.

Methods: A search was conducted, limited to the past 4 years (January 2016-April 2020), pertaining to published evidence of surgery for patients receiving emicizumab. Publications identified from the search were manually reviewed to determine studies and case reports relevant for inclusion.

Results: Identified literature and practical experience of the authors were used to build a consensus of practical recommendations for the concomitant administration of haemostatic agents during the perioperative period for elective surgery in patients with inhibitors who are receiving emicizumab.

Conclusions: The current evidence base indicates that surgery can be successfully performed in patients with inhibitors who are receiving emicizumab and that bypassing agents can be used concomitantly. Data from prospective studies are required to further support recommendations for haemostatic management of surgery in patients receiving emicizumab.

KEYWORDS
bypassing agents, emicizumab, FVIII inhibitors, haemophilia A, monitoring, surgery

1 | INTRODUCTION

People with haemophilia A may experience recurrent bleeding episodes into the joints that can result in chronic synovitis, progressive arthropathy, increased pain and reduced mobility.[1] For people with haemophilia who have severe joint impairment, surgical procedures may help to restore joint function and improve quality of life in cases where conservative intervention has failed.[1,2] Surgeries in people with haemophilia are typically managed with perioperative doses of factor concentrate, requiring planning from a specialised multidisciplinary team to prevent prolonged or excessive bleeding and optimise outcomes.[3,4]

The development of inhibitory antibodies to factor VIII (FVIII) is the most significant complication of haemophilia treatment and can result in increased morbidity, bleeding risk, joint damage and indication for surgical intervention.[5,6] For people with haemophilia and FVIII inhibitors, bypassing agents (BPAs)—including activated prothrombin complex concentrates (aPCC) and activated recombinant factor VII (rFVIIa)—and antifibrinolytic agents may be used during surgical procedures to maintain haemostasis.[6,7] The choice of BPA

Expert opinion recommendations for major orthopaedic surgery in patients with inhibitors, based on published evidence and clinical experience:

1. Recommendations in the context of major surgery require individualisation of doses based on the historical bleeding phenotype of the patient, experience of the surgical centre for treating patients receiving emicizumab, local guidelines and anticipated level of bleeding associated with the procedure.
    a. The requirement for administration of BPAs in combination with antifibrinolytics, or administration of antifibrinolytics alone, will also be dependent on these variables.
    b. Treatment principles for major surgery are applicable to both orthopaedic and non-orthopaedic procedures.
2. Administration of emicizumab:
    a. Emicizumab should be dosed as per the prescribed maintenance regimen throughout the pre-, peri- and post-operative period.
    b. Caution regarding emicizumab administration should be taken when more than one-third of whole blood volume is lost during surgery, because the distribution of emicizumab into the third extracellular compartment has not been described in detail.
    c. Further research should investigate the availability and/or benefit of re-dosing emicizumab during major procedures that require a transfusion.
3. Preoperative dosing recommendations for concomitant haemostatic agents:
    a. 90–120 μg/kg rFVIIa (single dose) + tranexamic acid 10 mg/kg intravenous (i.v.) (×4 doses) (OR tranexamic acid 25 mg/kg oral administration [×4 doses]).
4. Perioperative dosing recommendations for concomitant haemostatic agents:
    a. 90 μg/kg rFVIIa every 2 h.
    b. Adjust dosing according to bleed volume.
    ▪. In the event of excessive bleeding, increase the rFVIIa dose (maximum single dose should not exceed 270 μg/kg) or shorten the duration between rFVIIa doses.
    ▪. In the absence of bleeding, or presence of very minor bleeding, consider reducing rFVIIa dose (90 μg/kg every 3–4 h).
5. Post-operative dosing recommendations:
    a. Days 1–2 (0–48 h) post-procedure: 90 μg/kg rFVIIa every 2–3 h + tranexamic acid 10 mg/kg i.v. (×4 doses).
    b. Days 3–4 (48–96 h) post-procedure: 90 μg/kg rFVIIa every 4 h + tranexamic acid 10 mg/kg i.v. (×4 doses).
    c. Days 5–7 (96–168 h) post-procedure: 90 μg/kg rFVIIa every 6 h + tranexamic acid 10 mg/kg i.v. (×4 doses).
    d. In the event of excessive post-operative bleeding, increase the rFVIIa dose (maximum single dose should not exceed 270 μg/kg) or shorten the duration between rFVIIa doses.
    e. In the absence of bleeding, consider reducing the frequency of rFVIIa dosing.
6. Management of post-operative bleeds when patients are not responsive to rFVIIa:
    a. Individualised aPCC (<50 IU/kg per dose) every 8–12 h until bleeding is controlled.
    ▪. The safety and efficacy of concomitant administration of aPCC and tranexamic acid have been demonstrated previously in patients with inhibitors.[24] However, the prescribing information of aPCC advises that there is a possibility of thrombotic events if the agents are used together.[25] Therefore, until further research supports it, the use of concomitant aPCC and tranexamic acid to manage post-operative bleeds in patients receiving emicizumab who are not responsive to rFVIIa should be avoided if possible.
    b. If inhibitor titre is low (<5 Bethesda Units [BU]), high doses of FVIII could be used to achieve haemostasis.

to manage bleeding episodes may be influenced by access, safety, patient age and historical haemostatic response to treatment.[7] Both aPCC and rFVIIa have demonstrated haemostatic efficacy for the treatment of patients with inhibitors who are undergoing surgery.[7] However, there is a lack of standardised laboratory assays that have been demonstrated to effectively monitor haemostatic response to BPAs, and protocols for the dose and administration of BPAs vary between procedures and treatment centres.[7]

Emicizumab (Hemlibra®, F. Hoffmann-La Roche) is a bispecific monoclonal IgG_4 antibody that bridges activated factor IX (FIXa) and factor X (FX) to mimic the co-factor activity of FVIII and restore haemostasis in patients with FVIII inhibitors.[8,9] Although emicizumab prophylaxis has demonstrated efficacy for controlling haemostasis, the level of protection it offers means that patients may require additional administration of BPAs or clotting factor to control bleeding episodes and provide haemostatic cover during the perioperative period.[10–12]

The scarcity of published reports of surgery in patients treated with emicizumab, and the occurrence of thrombotic events following cumulative doses of aPCC in the HAVEN 1 emicizumab trial,[13] prompted The United Kingdom Haemophilia Centre Doctors' Organisation and the National Hemophilia Foundation's Medical and Scientific Advisory Council to release interim guidelines to mitigate the risk of adverse events when administering BPAs.[10,12] These recommendations for the treatment of breakthrough bleeds with BPAs suggest to avoid concomitant administration of aPCC unless no alternative BPA is available.[10,12] More recently, a practical guidance publication from Castaman et al.[14] for the management of patients with inhibitors on emicizumab prophylaxis in the emergency setting advised that low doses of aPCC may be considered to manage breakthrough bleeds in cases where patients do not respond to first-line treatment with rFVIIa. Furthermore, several French haemophilia networks collaborated to publish proposals for the management of bleeding and invasive procedures in patients with inhibitors treated with emicizumab, but acknowledged the lack of published evidence to provide formal guidelines.[15]

The number of patients treated with emicizumab is increasing, and with it, the need to provide guidance regarding the dose, administration and laboratory monitoring of BPAs in this situation. This article aims to review the evidence base around haemostatic coverage for patients with haemophilia A and inhibitors who are receiving emicizumab and undergoing surgery and provide practical recommendations in this area, informed by the published literature and the clinical experience of the authors.

2 | METHODOLOGY

2.1 | Literature search

To identify sources relevant for this review, a literature search was conducted pertaining to surgery in people with haemophilia A who received treatment with emicizumab. Corresponding with the first approval of emicizumab in December 2017,[16] a search of publications from 1 January 2016 to 31 April 2020 was performed in the electronic database PubMed (https://www.ncbi.nlm.nih.gov/pubmed), using the search term "emicizumab AND ("invasive" OR "procedure" OR "surg*")". The results were manually reviewed for relevance, and reference lists of the publications were reviewed to identify further articles related to the topic. To incorporate additional published evidence and further support recommendations for surgery in patients treated with emicizumab, a search of publications from global haemophilia congresses (the European Association for Haemophilia and Allied Disorders [EAHAD]; the International Society on Thrombosis and Haemostasis [ISTH]; the ISTH Scientific and Standardization Committee [ISTH SSC]; the World Federation of Hemophilia [WFH]; and the American Society of Hematology [ASH]) in the range 1 January 2016–31 April 2020 was performed, using the search term "emicizumab". The results were manually reviewed for relevance. A separate search of PubMed and global haemophilia congresses was performed to identify articles related to laboratory monitoring of emicizumab.

2.2 | Classification of 'major' vs 'minor' surgery

Surgical interventions in people with haemophilia are typically categorised as 'major' or 'minor' interventions, reflecting the anticipated bleeding risk associated with the procedure.[17] Owing to the variation in definitions for 'major' and 'minor' surgery between individual publications, the influence of the historical bleeding phenotype of the patient on surgery outcomes, and the anticipated duration and intensity of the procedure,[17] a decision was taken to classify interventions as 'major' or 'minor' procedures for this review as follows: 'major surgery': arthroplasty (including joint replacement, fusion and endoprosthesis), open reduction and internal fixation, abdominal surgery, thoracic surgery, neurological surgery,'–ectomy' procedures and '–otomy' procedures and 'minor surgery': central venous access device (CVAD) insertion/replacement/removal, haemorrhoid removal, biopsies of surface area, circumcision, dental procedures and radiosynovectomies.

3 | LITERATURE SEARCH RESULTS

The literature search initially identified 20 articles and 13 abstracts that were deemed potentially relevant for review and inclusion (Figure S1). The majority of publications identified from the literature search reported surgery in people with haemophilia and inhibitors. This is likely to be attributed to the majority of patients in the emicizumab clinical trials programme having an inhibitor and the initial regulatory approval of emicizumab being for use in inhibitor patients only. Orthopaedic procedures were the only type of major surgery for which published evidence in patients with inhibitors receiving emicizumab was available.

TABLE 1 Reports of major orthopaedic surgery in patients with inhibitors receiving emicizumab

	Patient	Surgery type	Perioperative dose			Management of complications	Resolution of surgical management
			Preoperative dose	Dose during surgery	Post-operative dose		
Case reports							
Anzej Doma et al. 2020[43]	50-year-old male with inhibitors on emicizumab loading regimen	Internal fixation for spiral fracture (non-elective)	94 μg/kg rFVIIa and 1 g tranexamic acid (immediately before surgery)	82 μg/kg rFVIIa every 3 h		No adverse events	Tapered decrease in frequency of rFVIIa over 15 days
Biron-Andreani et al. 2019[21]	60-year-old patient with inhibitors (low titre) on emicizumab maintenance regimen	Total hip arthroplasty (elective)	100 IU/kg pdFVIII (day of surgery)	Days 0–5: 100 IU/kg pdFVIII every 8 h		No adverse events	pdFVIII stopped 5 days after surgery due to increase in inhibitor titre
Biron-Andreani et al. 2019[21]	60-year-old patient with inhibitors (high titre) on emicizumab maintenance regimen	Total bilateral ankle arthroplasty (elective)	90 μg/kg rFVIIa (immediately before surgery)	90 μg/kg rFVIIa every 2 h (for 48 h), followed by 90 μg/kg rFVIIa every 3 h		rFVIIa dosing interval subsequently reduced to every 2 h to resolve knee swelling	rFVIIa stopped on Day 7 following surgery
Chou et al. 2019[22]	23-year-old patient with inhibitors (low titre) on emicizumab maintenance regimen	Open reduction and internal fixation of left femur (non-elective)	90 μg/kg rFVIIa (administered prior to surgery every 2 h to facilitate fluid resuscitation and transfusion)	Not specified	FVIII 100 IU/kg every 8 h, followed by FVIII 50 IU/kg every 8 h	FVIII administered as rescue medication to resolve left hip haematoma	Haematoma resolved. Tapered decrease of FVIII over 10 days
Kizilocak et al. 2019[11]	25-year-old male with inhibitors (high titre) on emicizumab maintenance regimen	Total right knee arthroplasty (elective)	200 μg/kg rFVIIa (immediately before surgery)	100 μg/kg rFVIIa every 2 h	100 μg/kg rFVIIa every 2 h	No adverse events	Tapered decrease in frequency of rFVIIa over 2 weeks
Santagostino et al. 2019[20]	56-year-old male with inhibitors (low titre) on emicizumab maintenance regimen	Right hip arthroplasty (non-elective)	98 μg/kg rFVIIa (immediately before surgery)	82 μg/kg rFVIIa every 3 h		pdFVIII administered as rescue medication to resolve right thigh haematoma	Haematoma resolved. Patient switched to 80 μg/kg rFVIIa every 4 h alongside tranexamic acid. Tapered decrease of rFVIIa over 6 days

(Continues)

TABLE 1 Continued

	Patient	Surgery type	Perioperative dose			Management of complications	Resolution of surgical management
			Preoperative dose	Dose during surgery	Post-operative dose		
Seaman et al. 2019[44]	54-year-old male with inhibitors (high titre) on emicizumab maintenance regimen	Total hip arthroplasty (elective)	180 μg/kg rFVIIa (immediately before surgery)	90 μg/kg rFVIIa every 3 h		No adverse events	Tapered decrease in frequency of rFVIIa over 2 weeks
Retrospective chart reviews							
Ebbert et al. 2019[23]	Patient with inhibitors on emicizumab maintenance regimen	Total hip arthroplasty	180 μg/kg rFVIIa	Not specified	90 μg/kg rFVIIa alternating with 5000 IU aPCC every 6 hrs (×45 doses), followed by 90 μg/kg rFVIIa every 2 h (×35 doses)	Post-operative bleeding managed with aPCC. Developed TMA and subsequent urethral abscess. Urethroplasty repair managed with porcine FVIII and RBC transfusion	Urethroplasty repair accomplished
Ebbert et al. 2019[23]	Patient with inhibitors on emicizumab maintenance regimen	Ankle fusion	20 IU/kg rFVIIIFc	Not specified	50 IU/kg rFVIIIFc (×1 dose), followed by 25 IU/kg rFVIIIFc (×4 doses)	No adverse event	rFVIIIFc stopped after ×4 doses at 25 IU/kg
Ebbert et al. 2019[23]	Patient with inhibitors on emicizumab maintenance regimen	Total hip arthroplasty	180 μg/kg rFVIIa	Not specified	90 μg/kg rFVIIa (×58 doses)	No adverse event	rFVIIa stopped after 58 doses

Abbreviations: aPCC, activated prothrombin complex concentrate; FVIII, factor VIII; pdFVIII, plasma-derived factor VIII; RBC, red blood cells; rFVIIa, activated recombinant factor VII; rFVIIIFc, recombinant factor VIII FC fusion protein; TMA, thrombotic microangiopathy.

TABLE 2 Reports of minor surgical procedures in patients with inhibitors receiving emicizumab

	Patient	Surgery type	Perioperative dose			Management of complications	Resolution of surgical management
			Preoperative dose	Dose during surgery	Post-operative dose		
Central venous access device procedures							
Batsuli et al. 2019[29]	15-month-old patient with inhibitors (high titre)	CVAD insertion	90 μg/kg rFVIIa	Not specified	90 μg/kg rFVIIa every 12 h, antifibrinolytic agents	No adverse events	Tapering dose of rFVIIa (×6 doses)
Batsuli et al. 2019[29]	16-month-old patient with inhibitors (low titre)	CVAD insertion	100 IU/kg rFVIII	Not specified	100 IU/kg rFVIII (×4 doses), antifibrinolytic agents	No adverse events	rFVIII stopped after 4 post-operative doses
Batsuli et al. 2019[29]	23-month-old patient with inhibitors (low titre)	CVAD insertion	100 IU/kg pdFVIII	Not specified	100 IU/kg rFVIII (×4 doses), antifibrinolytic agents	No adverse events	rFVIII stopped after 4 post-operative doses
Batsuli et al. 2019[29]	2-year-old patient with inhibitors (low titre)	CVAD removal	100 IU/kg pdFVIII	Not specified	100 IU/kg rFVIII, antifibrinolytic agents	No adverse events	rFVIII stopped after single post-operative doses
Ebbert et al. 2019[23]	Patient with inhibitors on emicizumab maintenance regimen	Port removal	No dose administered	Not specified	No dose administered	No adverse events	No BPAs or antifibrinolytics required
Ebbert et al. 2019[23]	Patient with inhibitors on emicizumab maintenance regimen	Port removal	No dose administered	Not specified	No dose administered	No adverse events	No BPAs or antifibrinolytics required
Ebbert et al. 2019[23]	Patient with inhibitors on emicizumab maintenance regimen	Port removal	No dose administered	Not specified	No dose administered	No adverse events	No BPAs or antifibrinolytics required
McCary et al. 2020[45]	4-year-old patient with inhibitors	Port removal	74 μg/kg rFVIIa (×1 planned dose)			No adverse events	No further BPAs or antifibrinolytics required
McCary et al. 2020[45]	4-year-old patient with inhibitors	Port removal	rFVIIa (×1 planned dose)		rFVIIa (×2 doses; unknown dose)	Swollen right chest post-operative	rFVIIa stopped after two post-operative doses
McCary et al. 2020[45]	5-year-old patient with inhibitors	Port removal	90 μg/kg rFVIIa (×1 planned dose)			No adverse events	No further BPAs or antifibrinolytics required
McCary et al. 2020[45]	7-year-old patient with inhibitors	Port removal	90 μg/kg rFVIIa (×1 planned dose)			No adverse events	No further BPAs or antifibrinolytics required
McCary et al. 2020[45]	8-year-old patient with inhibitors	Port removal	No dose administered			No adverse events	No BPAs or antifibrinolytics required

(Continues)

TABLE 2 (Continued)

	Patient	Surgery type	Perioperative dose			Management of complications	Resolution of surgical management
			Preoperative dose	Dose during surgery	Post-operative dose		
McCary et al. 2020[45]	9-year-old patient with inhibitors	Port removal	35 μg/kg rFVIIa (×2 planned doses)		No dose administered	No adverse events	No BPAs or antifibrinolytics required
Zimowski et al. 2018[46]	16-year-old patient with inhibitors (high titre)	CVAD removal	90 μg/kg rFVIIa	Not specified	90 μg/kg rFVIIa (single dose) 50 mg/kg aminocaproic acid every 8 h	Haematoma at prior CVAD site	Aminocaproic acid stopped after 3 days
Zimowski et al. 2018[46]	8-year-old patient with inhibitors (high titre)	PICC line removal	No dose administered	Not specified	No dose administered	No adverse events	No BPAs or antifibrinolytics required
Circumcision							
Barg et al. 2019[26]	<6-month-old male receiving emicizumab	Circumcision	Not specified	Not specified	rFVIIa and blood transfusion	Major post-procedural bleeding requiring blood transfusions and rFVIIa transfusions	rFVIIa and blood transfusion required to resolve bleed
Batsuli et al. 2019[29]	2-year-old male with inhibitors (low titre) on emicizumab maintenance regimen receiving ITI with rFVIII	Circumcision	100 IU/kg rFVIII	Not specified	100 IU/kg rFVIII	No adverse events	rFVIII stopped after single post-operative dose
Kavakli et al. 2020[47]	12-year-old male with inhibitors (high titre) on emicizumab maintenance regimen	Circumcision	Fibrin Glue (Beriplast, Behring), and tranexamic acid (applied for 7 days)			No adverse events	Tranexamic acid stopped after 7 days
Zulfikar et al. 2020[48]	10-year-old male with inhibitors (high titre) on emicizumab maintenance regimen	Circumcision	40 mg tranexamic acid received prior to surgery and continued for 10 days			No adverse events	Tranexamic acid stopped after 10 days
Dental							
Ebbert et al. 2019[23]	Patient with inhibitors on emicizumab maintenance regimen	Dental procedure	No dose administered	Not specified	No dose administered	Bleeding occurred	No post-operative treatment administered
Ebbert et al. 2019[23]	Patient with inhibitors on emicizumab maintenance regimen	Dental procedure	90 μg/kg rFVIIa	Not specified	90 μg/kg rFVIIa every 4 h (×3 doses) 50 mg/kg aminocaproic acid (×15 doses)	Bleeding occurred	Bleeding managed with rFVIIa and aminocaproic acid

(Continues)

TABLE 2 (Continued)

Patient	Surgery type	Perioperative dose		Post-operative dose	Management of complications	Resolution of surgical management
		Preoperative dose	Dose during surgery			
McCary et al. 2020[45,49] 27-year-old patient with inhibitors on emicizumab maintenance regimen	Dental implant	Aminocaproic acid (×12 doses)			No adverse event	No bleeding events or further BPA use required
McCary et al. 2020[45] 9-year-old patient with inhibitors on emicizumab maintenance regimen	Dental procedure	Aminocaproic acid			No adverse event	No bleeding events or further BPA use required
McCary et al. 2020[45] 8-year-old patient with inhibitors on emicizumab maintenance regimen	Dental extraction	66 IU/kg plasma-derived von Willebrand concentrate (×1 planned dose) and aminocaproic acid			No adverse event	No bleeding events or further BPA use required
Zimowski et al. 2018[46] 29-year-old patient with inhibitors (high titre) on emicizumab maintenance	Dental procedures (4 extractions; 1 alveoloplasty)	90 μg/kg rFVIIa	Not specified	No dose administered	No adverse event	No bleeding events or further BPA use required

Abbreviations: BPA, bypassing agent; CVAD, central venous access device; ITI, immune tolerance induction; pdFVIII, plasma-derived factor VIII; PICC, peripherally inserted central catheter; rFVIIa, activated recombinant factor VII; rFVIII, recombinant factor VIII.

4 | RECOMMENDATIONS FOR SURGERY IN PATIENTS RECEIVING EMICIZUMAB

4.1 | Major surgery

Use of haemostatic agents to manage major orthopaedic surgery was observed during the HAVEN 1–4 trials, where the majority (15/18; 83.3%) of major surgeries (including five arthroplasty and three synovectomy procedures) were managed with prophylactic coagulation factor,[18] although it is unclear what proportion of these patients had inhibitors. During the HAVEN 1 trial assessing once-weekly emicizumab prophylaxis in patients ≥12 years with inhibitors, two patients underwent major orthopaedic surgery (total hip arthroplasty and knee arthroscopy), where rFVIIa was also used perioperatively.[19]

Procedures classified as 'major surgery' for which there were published reports in the literature in patients with inhibitors receiving emicizumab included the following orthopaedic interventions: arthroplasty (including joint replacement, fusion and endoprosthesis) and open reduction and internal fixation (n = 10; Table 1). The majority of these procedures were managed with a preoperative dose of between 90 and 200 μg/kg rFVIIa to maintain haemostasis. During the post-operative period, rFVIIa was often administered every 2–3 h at doses of between 80 and 100 μg/kg, followed by tapered rFVIIa doses over 2 weeks in the absence of bleeding. For procedures where swelling or bleeding events occurred, administration of further doses of rFVIIa or rescue with FVIII (in patients with low-titre inhibitors) was used to resolve bleeding.[20–23]

There were several cases for which bleeding was managed with haemostatic agents other than rFVIIa. A patient undergoing total hip arthroplasty was managed with pre- and post-operative doses of plasma-derived FVIII. There were no adverse events; however, the use of FVIII in this patient led to an increase in inhibitor titre and the cessation of plasma-derived FVIII treatment. Therefore, FVIII may have a role for surgery management in patients with low-titre inhibitors.[21] One surgery case administered alternating doses of 90 μg/kg rFVIIa and 5000 IU aPCC every 6 h for a total of 45 doses to resolve a post-operative bleed. Despite discontinuing treatment with emicizumab 30 days prior to surgery, a thrombotic microangiopathy event occurred in association with aPCC use.[23] This outcome supports guidance from MASAC to apply a 6-month risk-mitigation period following emicizumab discontinuation to reduce the risk of aPCC interacting with residual plasma levels of emicizumab.[12,23]

4.2 | Minor surgery

Procedures classified as 'minor surgery' for which there were published reports in patients with inhibitors receiving emicizumab included the following interventions: CVAD insertion/replacement/removal (n = 15), circumcision (n = 4) and dental procedures (n = 6; Table 2). Further evidence for minor surgery was observed during HAVEN 1, where a total of 11 minor surgeries (including dental

procedures, CVAD procedures, radiosynovectomy and endoscopy) were performed that required perioperative administration of rFVIIa.[19]

4.2.1 | Central venous access device procedures

Insertion, removal or replacement of a CVAD are common procedures for patients requiring regular infusions of FVIII or BPA. Most patients receiving emicizumab undergoing CVAD replacement/removal received management with antifibrinolytic agents, and few experienced post-operative bleeds. Furthermore, Barg et al. reported two minor surgeries of central venous line extraction in paediatric patients with inhibitors that were managed without BPAs.[26] Surgery cases in patients with inhibitors from HAVEN 1 and interim reports from HAVEN 2 reported a total of nine CVAD insertion/replacement/removal procedures in seven patients. Of these, four procedures were managed with BPAs, of which none had post-operative bleeding. The remaining five procedures were managed without BPAs, and post-operative bleeds were observed in one of them.[27]

4.2.2 | Circumcision

There are various cultural and medical indications for circumcision. In the context of haemophilia, circumcision can be challenging due to increased bleeding risk with a procedure that is carried out predominantly in paediatric patients.[28] Case studies for patients with inhibitors receiving emicizumab suggest that circumcision may be managed with tranexamic acid alone. For a patient with low-titre inhibitors, the procedure was managed with two single doses of 100 IU/kg rFVIII.[29] However, one circumcision in a paediatric patient <6 months old with inhibitors was complicated by substantial post-operative bleeding that required management with blood transfusions and rFVIIa.[26]

4.2.3 | Dental surgery

Maintenance of oral health is important for people with haemophilia, as routine dental treatments often induce bleeding, which can lead to more severe complications.[30,31]

Existing guidelines may influence how invasive dental procedures are managed in people with bleeding disorders, including haemophilia.[31] The case reports and retrospective reviews identified suggest that the requirement and dose of BPAs and antifibrinolytic agents for the management of dental surgery vary between invasive procedures.

For dental procedures, the HAVEN 1 trial and interim data from the HAVEN 2 trial of emicizumab prophylaxis in paediatric patients with inhibitors reported a total of six tooth extraction procedures in five patients. Of these six procedures, two were managed with BPAs, with one patient experiencing post-operative bleeding. The remaining four surgeries were managed without BPAs, with post-operative bleeding observed for three of them.[27] This variability in treatment reflects the range of complexity of dental procedures, which may sometimes be classified in the literature as 'major' surgery, depending on type and number of teeth being operated on.[17]

Expert opinion recommendation for minor surgery in patients with inhibitors, based on published evidence and clinical experience:

1. Recommendations in the context of minor surgery require individualisation of doses based on the historical bleeding phenotype of the patient, experience of the surgical centre for treating patients receiving emicizumab, local guidelines and anticipated level of bleeding associated with the procedure.
    a. The requirement for administration of BPAs in combination with antifibrinolytics, or administration of antifibrinolytics alone, will also be dependent on these variables.
2. Administration of emicizumab:
    a. Emicizumab should be dosed as per the prescribed maintenance regimen throughout the pre-, peri- and post-operative period.
3. Preoperative dosing recommendations for concomitant haemostatic agents:
    a. Administration of BPAs should be considered on an individual basis, and in some cases, no BPAs may be required.
    b. If BPAs are required, use of 90 μg/kg rFVIIa (single dose) and/or tranexamic acid 10 mg/kg i.v. (×4 doses) is recommended.
4. Post-operative dosing recommendations:
    a. 90 μg/kg rFVIIa (single dose) and/or tranexamic acid 10 mg/kg i.v. (×4 doses).
    b. In the event of excessive post-operative bleeding, an additional 90 μg/kg rFVIIa may be considered.
    c. If very minor post-operative bleeding or no bleeding is observed, no intervention may be required.
5. Management of post-operative bleeds when patients are not responsive to rFVIIa:
    a. Individualised low doses of aPCC (<50 IU/kg per dose) every 8–12 h until bleeding is resolved.
    b. If inhibitor titre is low (<5 BU), high doses of FVIII could be used to achieve haemostasis.

4.3 | Emergency surgery

Patients on emicizumab prophylaxis may present with trauma or excessive bleeding that requires emergency intervention. The authors are in agreement with previous recommendations developed by Castaman et al.[14] for emergency surgical management in people with haemophilia A and inhibitors who are receiving treatment with emicizumab. These guidelines advise the emergency unit to immediately contact the haemophilia treatment centre (HTC) for guidance on the administration of haemostatic agents to manage emergency surgery. Dosing recommendations include immediate administration of rFVIIa before contacting the HTC in the event of major trauma or urgent surgery, avoidance of aPCC use unless no alternative option is available, and maintenance of the therapeutic schedule of emicizumab unless advised otherwise by the HTC.[14]

5 | MONITORING

Despite some guidelines recommending that regular laboratory monitoring of emicizumab activity may not be required during emicizumab prophylaxis,[12] it is advisable to monitor the haemostatic potential of emicizumab and concomitant administration of BPAs in the context of surgery and breakthrough bleeds to mitigate the risk of adverse thrombotic events.[32,33] Due to the lack of structural and functional homology to FVIIIa, emicizumab is expected to demonstrate different interactions on coagulation assays, compared with native FVIII.[34]

5.1 | Measuring FVIII activity and inhibitor titre

Emicizumab interferes with one-stage assays and chromogenic assays designed with human proteins, making these less suitable for the measurement of FVIII activity.[32,34–38] The WFH Guidelines (3rd Edition, 2020) instead recommend the use of a chromogenic FVIII assay containing bovine FX to measure FVIII activity and inhibitor levels in patients receiving emicizumab.[39]

5.2 | Thrombin generation assay

The thrombin generation assay (TGA) has been assessed for its ability to estimate the haemostatic activity of emicizumab in comparison with FVIII.[34] Two case reports of surgery in patients receiving emicizumab described successful use of the TGA to determine the clinical course of surgery and individualisation of BPA use.[11,40] However, the major orthopaedic surgery reported by Santagostino et al.[20] concluded that the TGA was unable to predict the clinical course of bleeding. The conflicting results reported in the literature suggest that further assessment into the validity of using the TGA to tailor treatment in patients receiving emicizumab is required.

5.3 | Clot waveform analysis

An adjusted clot waveform analysis with mixed reagents of prothrombin time/aPTT demonstrated the ability to quantify the coagulation potential of emicizumab alongside concomitant use of FVIII or BPAs.[41] In the context of surgery, verification of this technique may allow for closer monitoring of haemostatic potential of emicizumab and concomitant agents to mitigate the risk of thrombotic events.

6 | CONCLUSIONS

The evidence base for surgery in patients who are receiving treatment with emicizumab continues to grow, which may be due to more widespread availability of emicizumab and its approval for use in patients with haemophilia A both with and without inhibitors.[16,42] Despite the potential requirement for administration of additional haemostatic agents to prevent and control bleeding, surgery should be available to all patients receiving emicizumab. The recommendations presented here for dosing and administration of BPAs during the perioperative period build on previous guidelines for patients treated with emicizumab and are based on published evidence and the practical experience of the authors.[10,12,14,15,38] At variance with previous guidelines, the primary focus of this publication is for elective surgery in people with haemophilia and inhibitors who are treated with emicizumab.

Although clinical experience with emicizumab is increasing, the recommendations presented here are limited by the majority of surgical procedures performed in the HAVEN programme not being published in full at the time of the analysis. More extensive evidence is required to further support recommendations and help to develop international consensus guidelines for the management of surgery in patients receiving emicizumab. Prospective data collection from existing registries of patients receiving emicizumab or the establishment of a new registry endorsed by an international haemophilia organisation should generate further evidence for surgery in the real-world setting. Furthermore, a standardised protocol for the measurement of surgery outcomes and data collection in prospective trials would allow meaningful comparison of data between studies and case reports.

In the absence of tools for monitoring the haemostatic activity of BPAs, recommendations for effective dosing and administration of BPAs during the surgery period have been reliant on experience in published case reports and clinical data. Investigation into the utility of the TGA to assess emicizumab activity is required to verify its performance and as a predictor of bleeding complications. It should be emphasised within the scientific community that aPTT values are shortened in the presence of emicizumab, and aPTT-based coagulation tests may be misinterpreted due to an overestimation of FVIII activity. In the context of our current understanding of emicizumab, a universal laboratory monitoring tool should be developed to standardise measurement of the haemostatic potential of emicizumab

alongside concomitant administration of BPAs, to mitigate the risk of adverse events.

Although further research is required to validate the dose, administration and laboratory monitoring of BPAs, the current evidence base suggests that surgery can be successfully performed in patients with haemophilia A and inhibitors who are receiving treatment with emicizumab.

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CONFLICT OF INTEREST

VJY has received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or honoraria for consulting, and/or funds for research from Bayer, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi and Takeda. ECRM has received honoraria for speaking and/or honoraria for consulting, and/or funds for research from Bayer, Novo Nordisk, Pfizer, Roche, Sobi and Takeda. TM serves on advisory boards for Baxalta/Shire/Takeda, Bayer, Novo Nordisk, Chugai and Pfizer; has received educational and investigational support from Chugai and Novo Nordisk; and has received honorarium from Bayer, Bioverativ/Sanofi, Chugai, CSL Behring, Novo Nordisk and Shire/Takeda. PAH has received grant/research support from Bayer, Octapharma, Pfizer, Shire and Sobi; and has received honoraria for consulting from Bayer, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Shire and Sobi.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the analysis and interpretation of the literature; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data sets were generated or analysed during the current study.

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REFERENCES

1. Knobe K, Berntorp E. Haemophilia and joint disease: pathophysiology, evaluation, and management. *J Comorb*. 2011;1:51-59.
2. Morfini M, Benson G, Jiménez-Yuste V, et al. Tailoring care to haemophilia patients' needs: which specialty and when? *Blood Transfus*. 2015;13:644-650.
3. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19:e1-e47.
4. Escobar MA, Brewer A, Caviglia H, et al. Recommendations on multidisciplinary management of elective surgery in people with haemophilia. *Haemophilia*. 2018;24:693-702.
5. Walsh CE, Jiménez-Yuste V, Auerswald G, Grancha S. The burden of inhibitors in haemophilia patients. *Thromb Haemost*. 2016;116(Suppl 1):S10-S17.
6. Ju HY, Jang HL, Park YS. The efficacy of bypassing agents in surgery of hemophilia patients with inhibitors. *Blood Res*. 2015;50:173-178.
7. Holme P. Surgery in Inhibitor Patients. In: Lee CABE, Hoots WK, eds. *Textbook of Hemophilia*. 3rd Ed. New Jersey, NJ. John Wiley & Sons Ltd; 2014:213-217.
8. Kitazawa T, Esaki K, Tachibana T, et al. Factor VIIIa-mimetic cofactor activity of a bispecific antibody to factors IX/IXa and X/Xa, emicizumab, depends on its ability to bridge the antigens. *Thromb Haemost*. 2017;117:1348-1357.
9. Young G, Liesner RI, Chang T, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. *Blood*. 2019;134:2127-2138.
10. Collins PW, Liesner R, Makris M, et al. Treatment of bleeding episodes in haemophilia A complicated by a factor VIII inhibitor in patients receiving emicizumab. Interim guidance from UKHCDO inhibitor working party and executive committee. *Haemophilia*. 2018;24:344-347.
11. Kizilocak H, Yukhtman CL, Marquez-Casas E, Lee J, Donkin J, Young G. Management of perioperative hemostasis in a severe hemophilia A patient with inhibitors on emicizumab using global hemostasis assays. *Ther Adv Hematol*. 2019;10:2040620719860025.
12. Recommendation on the use and management of emicizumab-kxwh (Hemlibra®) for hemophilia A with and without inhibitors. https://www.hemophilia.org/sites/default/files/document/files/255Emicizumab.pdf. Accessed March 2020.
13. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017;377:809-818.
14. Castaman G, Santoro C, Coppola A, et al. Emergency management in patients with haemophilia A and inhibitors on prophylaxis with emicizumab: AICE practical guidance in collaboration with SIBioC, SIMEU, SIMEUP, SIPMeL and SISET. *Blood Transfus*. 2020;18:143-151.
15. 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.
16. Hemlibra® prescribing information. https://www.gene.com/download/pdf/hemlibra_prescribing.pdf. Accessed March 2020.
17. Solimeno LP, Escobar MA, Krassova S, Seremetis S. Major and minor classifications for surgery in people with hemophilia: a literature review. *Clin Appl Thromb Hemost*. 2018;24:549-559.
18. Santagostino E, Oldenburg J, Chang T, et al. Surgical experience from four phase III studies (HAVEN 1–4) of emicizumab in persons with haemophilia A (PwHA) with or without FVIII inhibitors. Oral presentation OC 60.1 presented at ISTH 2019, Melbourne, Australia. *Res Pract Thromb Haemost*. 2019;3(Suppl 1):115.

19. Levy GG, Asikanius E, Kuebler P, Benchikh El Fegoun S, Esbjerg S, Seremetis S. Safety analysis of rFVIIa with emicizumab dosing in congenital hemophilia A with inhibitors: experience from the HAVEN clinical program. *J Thromb Haemost*. 2019;17:1470-1477.
20. Santagostino E, Mancuso ME, Novembrino C, Solimeno LP, Tripodi A, Peyvandi F. 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.
21. Biron-Andreani C, Diaz-Cau I, Navarro R, et al. Management of surgery in haemophilia A patients with inhibitors during emicziumab prophylaxis. Poster PB0319 presented at ISTH 2019, Melbourne, Australia. *Res Pract Thromb Haemost*. 2019;3(Suppl 1):312.
22. Chou S-C, Nagami S, Lin S-W, Tien H-F. Successful management with a major trauma caused by vehicle accident in a severe hemophilia A patient with inhibitor under emicizumab treatment. Poster PB1405 presented at ISTH, Melbourne, Australia. *Res Pract Thromb Haemost*. 2019;3(Suppl 1):422.
23. Ebbert PT, Xavier F, Seaman CD, Ragni MV. Emicizumab prophylaxis in patients with haemophilia A with and without inhibitors. *Haemophilia*. 2020;26:41-46.
24. Holmstrom M, Tran H, Holme P. Combined treatment with APCC (FEIBA®) and tranexamic acid in patients with haemophilia A with inhibitors and in patients with acquired haemophilia A - a two-centre experience. *Haemophilia*. 2012;18:544-549.
25. Feiba® prescribing information. https://www.shirecontent.com/PI/PDFs/FEIBA_USA_ENG.pdf. Accessed January 2021
26. Barg AA, Avishai E, Budnik I, et al. Emicizumab prophylaxis among infants and toddlers with severe hemophilia A and inhibitors-a single-center cohort. *Pediatr Blood Cancer*. 2019;66:e27886.
27. Kruse-Jarres R, Callaghan MU, 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). Presented at ASH, Atlanta, GA, USA. *Blood*. 2017;139 (Suppl 1):89.
28. Seck M, Sagna A, Guéye MS, et al. Circumcision in hemophilia using low quantity of factor concentrates: experience from Dakar, Senegal. *BMC Hematol*. 2017;17:8.
29. Batsuli G, Zimowski KL, Tickle K, Meeks SL, Sidonio RF Jr. Immune tolerance induction in paediatric patients with haemophilia A and inhibitors receiving emicizumab prophylaxis. *Haemophilia*. 2019;25:789-796.
30. Shastry SP, Kaul R, Baroudi K, Umar D. Hemophilia A: dental considerations and management. *J Int Soc Prev Community Dent*. 2014;4:S147-S152.
31. Anderson JAM, Brewer A, Creagh D, et al. Guidance on the dental management of patients with haemophilia and congenital bleeding disorders. *Br Dent J*. 2013;215:497-504.
32. Yada K, Nogami K. Spotlight on emicizumab in the management of hemophilia A: patient selection and special considerations. *J Blood Med*. 2019;10:171-181.
33. Sjöström A, Långström S, Ranta S, et al. Laboratory measurement of emicizumab first "real-life" experience from Karolinska University laboratory. Poster P003 presented at EAHAD, The Hague, The Netherlands. *Haemophilia*. 2020;26:28.
34. Aleman MM, Leksa NC, Peters R, Salas J. Assay challenges (and opportunities) with non-factor VIII therapies for hemophilia A. *Expert Rev Mol Diagn*. 2019;19:1-3.
35. Adamkewicz JI, Chen DC, Paz-Priel I. Effects and interferences of emicizumab, a humanised bispecific antibody mimicking activated Factor VIII cofactor function, on coagulation assays. *Thromb Haemost*. 2019;119:1084-1093.
36. Bowyer A, Kitchen S, Maclean R. The effect of emicizumab on assays of factor VIII activity in severe haemophilia A patients and artificially spiked plasma. Poster P027 presented at EAHAD, The Hague, The Netherlands. *Haemophilia*. 2020;26:49.
37. Jennings I, Kitchen D, Maclean R, et al. Assays performed on samples containing emicizumab - data from a multicentre study of UK NEQAS Blood Coagulation (BC) laboratories. Poster PB1312 presented at ISTH, Melbourne, Australia. *Res Pract Thromb Haemost*. 2019;3(Suppl 1):206-207.
38. 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.
39. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia. *Haemophilia*. 2020;26(Suppl 6):1-158.
40. Dargaud Y, Lienhart A, Janbain M, Le Quellec S, Enjolras N, Negrier C. Use of thrombin generation assay to personalize treatment of breakthrough bleeds in a patient with hemophilia and inhibitors receiving prophylaxis with emicizumab. *Haematologica*. 2018;103:e181-e183.
41. Nogami K, Matsumoto T, Tabuchi Y, et al. Modified clot waveform analysis to measure plasma coagulation potential in the presence of the anti-factor IXa/factor X bispecific antibody emicizumab. *J Thromb Haemost*. 2018;16:1078-1088.
42. Hemlibra®: summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/hemlibra-epar-product-information_en.pdf. Accessed March 2020.
43. Anzej Doma S, Zupan I, Fink M, Pompe B, Rener K. Emicizumab use in major orthopedic surgery-first experience in slovenia, a case report. Poster P180 presented at EAHAD, The Hague, The Netherlands. *Haemophilia*. 2020;26:120.
44. Seaman CD, Ragni MV. Emicizumab use in major orthopedic surgery. *Blood Adv*. 2019;3:1722-1724.
45. McCary I, Guelcher C, Kuhn J, et al. Real-world use of emicizumab in patients with haemophilia A: bleeding outcomes and surgical procedures. *Haemophilia*. 2020;26(4):631-636. https://doi.org/10.1111/hae.14005
46. Zimowski KL, Batsuli GM, Reding MT, et al. Maintaining perioperative hemostasis in patients with severe hemophilia A and inhibitors receiving emicizumab prophylaxis. Presented at ASH, San Diego, CA, USA. *Blood*. 2018;132(Suppl 1):635.
47. Kavakli K, Balkan C, Karadas N, Erdener A. Circumcision operation without using by-passing agents in patient with high responder inhibitor while he was in weekly emicizumab prophylaxis. Poster P118 presented at EAHAD, The Hague, The Netherlands. *Haemophilia*. 2020;26:89.
48. Zulfikar B, Koc B, Kara C. Circumcision in haemophilia with inhibitors during emicizumab prophylaxis. Poster P070 presented at EAHAD, The Hague, The Netherlands. *Haemophilia*. 2020;26:61.
49. McCary I, Guelcher C, Kuhn J, et al. Peri-procedural management and outcomes of patients with hemophilia on emicizumab prophylaxis. Poster presented at ASH 2019, Orlando, FL, USA. *Blood*. 2019;134(Suppl 1):2396.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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