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SUPPLEMENT ARTICLE

# Managing invasive procedures in haemophilia patients with limited resources, extended half-life concentrates or non-replacement therapies in 2022

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## Abstract

New treatment possibilities and modalities are now available globally for patients with haemophilia requiring surgery or invasive procedures.

The first is the appropriate application of low-dose protocols of clotting factor concentrates (CFC) achieving adequate perioperative haemostasis in resources constraint environments. The increasing availability of CFC through humanitarian aid programs allows more invasive surgeries to be performed for which efficacy and safety data should be more widely collected and reported.

Second, extended half-life CFC that are increasingly available in many countries represent valuable alternatives to standard half-life products in surgical patients allowing reduced number of infusions and lower consumption, in particular for extended half-life factor IX.

Third, in the era of recently introduced nonfactor prophylaxis, some minor surgical procedures can now be performed without additional haemostatic treatment, others with few low-dose administrations of CFC or bypassing agents. Additional factor VIII/IX or recombinant activated factor VII has proven to be safe and effective in association with emicizumab for major surgeries and it was effectively given at low doses in association with fitusiran (including activated prothrombin complex concentrate). No thrombotic complications have been reported in the surgical setting so far. A multidisciplinary team/facility remains crucial to manage major surgery in patients on prophylaxis with these new agents.

KEYWORDS

concizumab, emicizumab, extended half-life concentrates, fitusiran, haemophilia, invasive procedures, limited resources, low–dose protocols, surgery

## 1 | INVASIVE PROCEDURES IN PATIENTS WITH HAEMOPHILIA WITH LIMITED RESOURCES: AN ALTERNATIVE MODEL

### 1.1 | Introduction

Patients with Haemophilia (PWH) may need surgical interventions or invasive procedures for haemophilia related complications or unrelated issues. Forty percent of PWH reside in low and middle income countries (LMIC) with limited resources.[1] Invasive procedures on PWH with limited resources are difficult and challenging. Limited resources include availability and accessibility to Haemophilia Comprehensive Care Centres (HCCC) and clotting factor concentrates (CFC).

International guidelines for CFC prophylaxis for PWH undergoing surgical procedures are well established but are not practical in resource constraint settings.[2–4] These guidelines were indeed not

  

**TABLE 1** Plasma factor peak level and duration of administration when there is significant resource constraint / low-dose practice pattern[2]

| | Haemophilia A | Haemophilia B |
|---|---|---|
| | Major surgeries / desired levels (IU/DL) | |
| Pre-operative | 60–80 | 50–70 |
| Days 1–3 | 30–40 | 30–40 |
| Days 4–6 | 20–30 | 20–30 |
| Days 7–14 | 10–20 | 10–20 |
| | Minor surgeries / desired plasma levels (IU/DL) | |
| Pre-operative | 40–80 | 40–80 |
| Post-Operative | | |
| Days 1–5 depending on type of procedure | 20–50 | 20–50 |

established on the basis of clinical trials and aim to achieve normal levels of haemostasis with large margins of safety. They also fail to define safe lower limits of haemostasis for invasive procedures in PWH.[5] The need to define lower limits of haemostasis is crucial in limited resource setting so that resources can be used optimally. The WFH guidelines from 2005 onward have mentioned the lower dose protocols which then become as defined as the higher dose protocols. However, no strong comparative efficacy data have been reported to date.

There is limited data from LMIC with limited resources with respect to PWH undergoing surgical / invasive procedures. We here try to map the perioperative haemostatic efficacy of low-dose CFC protocols (lower than international recommendations) for surgical prophylaxis and invasive procedures. As summarized hereafter, the limited literature shows that low-dose protocols are effective, reduce CFC consumption by 30% and do not increase the risk of haemorrhage.

## 1.2 | Low-dose protocols for invasive procedures

The first series using low-dose protocol was reported in 1994 from India.[6] Thirty-seven haemophilia patients (32 HA and five HB) patients underwent orthopaedic, general surgical, neurosurgical and cardiothoracic invasive procedures. The postoperative trough levels were maintained at 20–40% of factor VIII (FVIII) and between 15 and 30% for factor IX (FIX) for a minimum of 10 days. Haemostatic efficacy was well achieved. In 1998 another group from India described various kinds of surgery carried out with great success in 16 cases which included both severe and moderate haemophilia patients treated with modest amounts of factor concentrates and antifibrinolytic drugs.[7] This was further confirmed by Srivastava and colleagues who described the haemostatic management of 18 patients with severe haemophilia (11 HA and 7 HB) undergoing 20 major surgery procedures using lower than usually recommended levels of CFC therapy.[8] Mathew and colleagues on the basis of their own experience and published data concluded in 2005 that low-dose protocols are effective, reduce factor consumption by one third, and are not associated with a significantly increased risk of delayed hemorrhage.[5] The WFH Guidelines for Management of Hemophilia recommend similar replacement plan for limited resource situations (Table 1).[2] This is a very important statement as it recognizes low-dose protocols for factor replacement for postoperative haemostasis. More recently, a study from Senegal involving 26 children showed that a treatment protocol using low quantity of CFC (30 IU/kg FVIII 1 h before surgery, repeated after 24 and 48h (mean amount FVIII of 1743 IU (810–2340) with compressive dressing and tranexamic acid) was efficient in haemophilia patients who underwent circumcision.[9]

Orthopaedic surgeries are the most common surgeries for PWH also in LMIC. Lee et al. reported their experience in patients with fractures and use of external fixators.[10,11] Joint damage is very severe in PWH from LMIC because of inadequate CFC availability for prophylaxis so that many PWH need total knee replacement (TKR) or total hip replacement (THR) at young age. Until now, a group in India has collected data on 42 patients who underwent 84 bilateral simultaneous TKR using low dose of Eloctate (600 IU/kg over 14 days) (unpublished data). We have also performed nine coronary angioplasties in HA patients using a single dose FVIII 25 IU/Kg at the time of arterial puncture and no further dose was given. None of the patient had excessive bleeding (unpublished data, personal communication, S. APTE).

## 1.3 | Continuous infusion versus bolus infusions of CFC in resource constraint settings

Martinowitz et al. showed that instead of intermittent bolus infusions of CFC, continuous infusion (CI) allows to achieve a 30% reduction in CFC requirements.[12] Although CI could be attractive, there are certain logistic issues like the stability of products, the need for expensive infusion pumps and disposables, the requirement for more frequent factor assays that altogether increase the expenses. For these reasons, low-dose intermittent bolus replacement therapy appears easier and cheaper than CI and cost effective in resource constraint settings.

## 1.4 | Surgical procedures in haemophilia A patients with inhibitors

Very limited data is available in the literature from LMIC on this topic.[13] Bypassing agents are not available in enough quantities to

allow surgery in this setting. The management of a patient with high-responding FVIII inhibitors using low doses of activate prothrombin complex concentrate (aPCC) in the postoperative period was previously reported[14] but the literature on the use of bypassing agents in limited resources environments is scarce. This could however likely change in the future at least for minor surgical procedures with the availability of new agents such as emicizumab in the frame of donations programs.

### 1.5 | Discussion

Surgery in PWH should be carried out in established HCCCs where trained teams are available with laboratory back up. In LMIC availability and accessibility of trained teams is an important issue. Slowly and definitely the number of health professionals with an expertise in haemophilia is growing. Still the limited availability of CFC remains a major obstacle. It appears that adequate postoperative haemostasis can be achieved with lower doses of factor replacement protocols. There is however a need to collect more data in a systematic fashion as probably many surgical experiences from LMIC are not published.

Low-dose protocols with an optimal use of the limited available CFC potentially increase by two-fold compared to using standard replacement protocols the number of patients who can benefit from surgical procedures with a major impact on their quality of life than. The Humanitarian Aid Program of the WFH has definitely improved the CFC supply so that more surgical procedures can now be carried out throughout LMIC. Collecting and reporting these surgical data appears critically important.

Available but limited data suggest that there is no great difference in surgical haemostasis and outcomes using low dose as compared with standard recommended protocols. These observations raise a fundamental and so far unanswered question for both high income and LMIC: "What is the minimum factor level required for adequate surgical haemostasis and wound healing?"

## 2 | INVASIVE PROCEDURES WITH EXTENDED HALF-LIFE FVIII AND FIX CONCENTRATES

In patients with haemophilia, surgery and other invasive procedures represent a major challenge as they are inherently associated with the potential for excessive and uncontrolled bleeding. Most invasive procedures require intensified FVIII or FIX replacement to achieve and maintain haemostasis and adequate factor levels until wound healing is complete. Because of their relatively short half-life which is approximately 12 h for standard half-life FVIII (SHL-FVIII) and 18 h for standard half-life FIX (SHL-FIX), standard formulations of FVIII and FIX require frequent administration in the peri- and postoperative periods.

Recent major treatment advances in haemophilia include the development of new recombinant extended half-life (EHL) FVIII (EHL-rFVIII) and FIX (EHL-rFIX) products with improved pharmacokinetic (PK) properties that aim to reduce the burden of prophylaxis. Four EHL-rFVIII products have recently been approved, three obtained by pegylation (damoctocog alfa pegol/BAY 94-9027 – Jivi, rurioctocog alfa pegol/BAX 855 – Adynovate, turoctocog alfa pegol/N8-GP – Esperoct) and one by Fc-fusion (efmoroctocog alfa – Elocta/Eloctate). With respect to EHL-rFIX, three are currently approved, one obtained by glycopegylation (nonacog beta pegol – Refixia), one by albumin fusion (albutrepenonacog alfa – Idelvion) and one by Fc-fusion (eftrenonacog alfa – Alprolix). Pharmacokinetic studies in adults have shown a 1.2 to 2-fold increase in half-life of EHL-rFVIII compared to full-length factor VIII and a 4 to 6-fold increase in half-life for EHL-rFIX.[15] For prophylaxis, EHL-rFVIII and to a much greater extent EHL-rFIX products can be used to prolong the dosing interval or provide higher factor trough levels for longer periods.

The safety, efficacy and consumption of all EHL in limited number of patients undergoing surgery and invasive procedures have recently been evaluated in several pivotal trials including pegylated EHL-rFVIII,[16–18] Fc-Fused EHL-rFVIII,[19] Fc-fused EHL-rFIX,[20,21] albumin-fused EHL-rFIX[22] and pegylated EHL-rIX.[23]

As reviewed hereafter, the use of EHL concentrates impacts on the perioperative haemostatic management of surgery and invasive procedures compared SHL-FVIII/FIX. In all published studies, the levels of FVIII and FIX targeted pre and postoperatively when using EHL concentrates were not different from the guidelines-recommended ranges that have previously been defined with the use of SHL-FVIII/FIX.[2]

### 2.1 | EHL-rFVIII and surgery

Studies performed with the different EHL-rFVIII have demonstrated that these products are effective and well tolerated for the prevention and treatment of bleeds during major orthopaedic and non-orthopaedic surgeries as well as for other minor invasive procedure.[16–19] The efficacy and safety results were consistent with those previously reported for unmodified FVIII. No FVIII inhibitors, thromboembolic events or clinically significant safety issues were detected and reported in published studies.

Most patients received a median bolus between 50 and 60 IU/kg preoperatively. Very few patients needed intraoperative infusion. The total number of infusions on the day of the surgery varied between one (most patients) to three (minority of patients). Haemostatic control was assessed as good or excellent in most reported cases. In the immediate postoperative period, most patients required one infusion of EHL-rFVIII per day.

These studies demonstrated that less frequent infusions and reduced factor consumption were needed to cover surgery with EHL-rFVIII compared to SHL-FVIII. Considering the wide variability in the types of surgeries, differences in local practices as well as distinctive ways information about FVIII usage was collected across studies, it is challenging to make comparisons across different products regarding FVIII consumption and frequency of infusions. However, there is no objective reason to suspect that the different EHL-rFVIII that show a very similar half-life prolongation would have different properties in this setting.

The ability to measure FVIII activity is of paramount importance for the preparation and management of major invasive procedures. Considering the high intraindividual variability in pharmacokinetics, preoperative PK evaluation could be considered. More importantly, FVIII should be measured daily postoperatively to adapt the treatment regimen.

Compared to adult and adolescent subjects, dosing on the day of surgery appeared to be higher (higher initial dose or greater need to provide a second infusion to prevent bleeding) in paediatric patients reflecting the well-known shorter half-life of FVIII in children compared to adults.[19]

### 2.2 | EHL-rFIX and surgery

Studies performed with the different EHL-rFIX have demonstrated that these products are effective and well tolerated for the prevention and treatment of bleeds during major orthopaedic and non-orthopaedic surgeries as well as for other minor procedure.[20–23] The efficacy and safety results were consistent with those previously reported for unmodified FIX. No FIX inhibitor, thromboembolic events or clinically significant safety issues were detected and reported in published studies.

Most patients received a median bolus between 80 and 90 IU/kg preoperatively. Most patients require one to three doses of EHL-rFIX on the day of surgery. Haemostatic control was assessed as good or excellent in most cases. In the postoperative period, the majority of patients were dosed approximately every 2 days to maintain the desired FIX activity level. This is in contrast with SHL-FIX which is required to be dosed at least daily to maintain haemostasis. As a result, EHL-rFIX concentrates allow major surgical interventions in patients with HB with significantly reduced concentrate consumption and infrequent injections as reported with SHL-FIX.

### 2.3 | EHL-rFVIII and continuous infusion

Conventional FVIII and FIX are often administered via CI during surgery and the postoperative period in order to maintain the appropriate factor levels. Since EHL-rFIX products have a much longer half-life than EHL-rFVIII, bolus infusions represent the treatment modality of choice in patients with HB since they can maintain adequate and stable FIX levels with bolus injections.

Regarding EHL-rFVIII, there has been a report of the successful use of CI of Fc-Fused rFVIII.[24] The lower rate of continuous infusion during steady state at 3 IU/kg/h of Fc-Fused rFVIII versus 5 IU/kg/h on SHL-FVIII aiming at the same FVIII target levels suggested a trend toward lower FVIII consumption, likely reflecting the accumulation of EHL-rFVIII in comparison to SHL-FVIII. The clinical advantages of CI are maintenance of constant FVIII levels and the ability to monitor levels at any time, rather than having to test just before bolus infusions. The disadvantages are the need for extra intravenous access for blood sampling. These aspects are similar for SHL-FVIII and EHL-rFVIII concentrates. There might be some concerns about the stability of the different EHL-rFVIII when administered by CI.

### 2.4 | Non-severe haemophilia and haemophilia carriers

The use of EHL-rFVIII and EHL-rFIX has mainly been studied and reported in patients with severe haemophilia undergoing surgery or invasive procedures. However, although evidence is still limited, the use EHL-rFIX in particular could be beneficial in patients with nonsevere HB undergoing invasive procedures who could reach and maintain prolonged haemostasis with a very limited number of infusions. Similarly, successful use of EHL-rFIX has been recently reported in carriers of HB with FIX deficiency requiring invasive procedure (delivery, surgery).[25]

### 2.5 | Low- and middle-income countries

Through the WFH humanitarian aid program, an increasing number of patients in LMIC have now access to EHL-rFVIII and rFIX concentrates that are used for surgery. Data on the use of these concentrates is currently being collected in the frame of the World Bleeding Disorders Registry of the WFH.

### 2.6 | Conclusions

The perioperative use of EHL-rFVIII and EHL-rFIX in patients undergoing surgery is effective, safe and well tolerated. These concentrates enable in most patients fewer infusions and reduced consumption and potentially allow earlier patient discharge, in particular for patients with HB.

Close monitoring of FVIII and FIX levels is however mandatory, certainly in the peri- and immediate postoperative period using the appropriate assays, as patients might require repeated bolus. More real-life data should be collected using standardized protocols to better define the ideal modalities of use of EHL-rFVIIII and FIX in both high and LMIC.

## 3 | INVASIVE PROCEDURES IN THE ERA OF NON-FACTOR REPLACEMENT THERAPY

### 3.1 | Introduction

New therapeutic approaches, able to trigger coagulation activation and thrombin generation not relying on replacement of the missing clotting factor, have been developed for bleeding prevention in inhibitor and noninhibitor PWH.[26] Of these nonreplacement therapies one is already available in the market and others are at advanced stages of clinical investigation.[26]

All these agents are administered subcutaneously, however they have different mechanisms of action to trigger coagulation activation and enhance thrombin generation. In fact, emicizumab (see below) is able to mimick the cofactorial function of FVIII, while fitusiran and anti-TFPI antibodies (see below) inhibit natural anticoagulant proteins as antithrombin or TFPI thus shifting the balance of haemostasis toward a procoagulant effect.[26]

Of note all these novel therapeutics have been designed to act as prophylactic agents able to prevent the majority but not all spontaneous bleeding episodes. Moreover, they cannot be used to control acute breakthrough bleeds or to prevent perioperative bleeding complications. In this light, concomitant use of other haemostatic agents as bypassing agents (BPAs: activated prothrombin complex concentrate [aPCC] or recombinant activated factor VII [rFVIIa]) or replacement therapies (i.e., FVIII or FIX concentrates) is required.[26]

According to the different mechanisms of action, the safety and efficacy profiles of these novel drugs vary and, consequently, the use in the perioperative setting should be investigated for each single agent. Indeed, the surgical setting represents a challenge due to the concomitant risk of bleeding and thrombotic complications, especially in inhibitor patients in whom bypassing therapy is used. To date, limited information on surgical management of PWH on prophylaxis with fitusiran and anti-TFPI is available from clinical trials.[27–29] On the other hand, more data have been collected and published on the surgical management of patients on emicizumab prophylaxis both during the clinical trial program[30–32] and in the real-world setting.[33–47]

## 3.2 | Perioperative management of PWH treated with emicizumab

Emicizumab is a humanized bispecific monoclonal antibody which bridges activated FIX and FX thus favouring FX activation and subsequent thrombin generation, thus mimicking the physiologic function of activated FVIII.[48] The drug has been approved internationally for bleeding prevention in PwHA of all ages with and without inhibitors. Overall, the clinical trial program showed a large proportion of patients who did not experience any bleeding episodes already after the first 24 weeks of emicizumab prophylaxis[49–52] and further increase of such proportion was observed over approximately 3 years of additional follow-up.[53]

During the phase 3 study, thrombotic events including thrombotic microangiopathy (TMA) were observed in five inhibitor patients who received concomitant high doses of aPCC (> 100 U/kg per day, > 24 h) to treat breakthrough bleeds.[49] Since then, guidelines have been implemented to recommend rFVIIa use as first line concomitant bypassing therapy in patients on emicizumab prophylaxis and, if possible, avoid aPCC or use it at the lowest doses for the management of breakthrough bleeds and/or invasive procedures.[54–59] On the other hand, no thrombotic adverse events have been described in patients without inhibitors receiving FVIII concentrates at standard doses in association with emicizumab prophylaxis. This might be related to the 10-fold higher affinity of FVIII for FIX and FX substrates which results in a transient displacement of emicizumab without additive haemostatic effect.[60] In this light for patients without inhibitors on emicizumab prophylaxis who undergo invasive procedures standard FVIII treatment regimens can be applied.[58,61–62]

Across the HAVEN program, 214 minor and 19 major surgeries were performed.[31] The majority of minor interventions were dental and central venous access device (CVAD) procedures. Of those, 141 (66%) were performed without additional preoperative haemostatic treatment and 128 of them (91%) did not result in treated postoperative bleeds. Of the 73 (34%) procedures managed with preoperative haemostatic treatment, 64 (88%) had no treated postoperative bleeds. Overall, treated bleeding complications followed most commonly dental procedures (14/63, 22%) irrespective of preoperative prophylaxis.[31] Of the 19 major surgeries, 16 (84%) were managed with prophylactic coagulation factor without postoperative bleed in 15 (94%). The three major surgeries managed without preoperative haemostatic prophylaxis were not complicated by bleeding. No thrombotic complications or deaths were reported.[31] With respect to perioperative treatment performed for these procedures, FVIII was given at standard doses in noninhibitor patients while rFVIIa was the BPA used in all inhibitor patients, but one case who underwent laparoscopic appendectomy after a single dose of aPCC (49.7 U/kg).[30–31]

Four detailed reports of major procedures (two arthroplasties, one excision of a thigh pseudotumor and one open laparotomy for duodenal ulcer) performed in inhibitor patients during the trial program were published.[35–36,63] One patient received a low-dose rFVIIa regimen (100 mcg/kg preoperatively followed by 80 mcg/kg every 3 h) for hip replacement and had a bleeding on postoperative day 1 which was controlled by FVIII treatment (115 IU/kg by bolus followed by continuous infusion at 3.3-4 IU/kg/h; inhibitor titre: 2 BU/ml).[35] The other case underwent knee replacement and was successfully treated with higher doses of rFVIIa (200 mcg/kg preoperatively followed by 100 mcg/kg every 2 h on postoperative day 1, subsequently tapered to every 3, 4 and 6 h on days 2, 3 and 4, respectively).[36] The pseudotumor excision was performed by using FVIII continuous infusion over 14 days (preoperative inhibitor titre: .6 BU/ml) without requirement of bypassing agents as inhibitor titre raised to 8.9 BU/ml on postoperative day 15; for the open laparotomy to treat a duodenal ulcer uncontrollable endoscopically, rFVIIa was used over 16 postoperative days without complications.[63] Recently, also the surgical experience in patients with inhibitors enrolled in the phase IIIb STASEY trial has been reported.[32] Overall, 56 minor (20, 36% dental procedures) and 22 major surgeries were performed. Among minor procedures 24 (43%) were performed with additional preoperative prophylaxis resulting in six (25%) treated postoperative bleeds (three following dental procedures), while five (14%) treated postoperative bleeds (two following dental procedures) followed 32 minor procedures performed without preoperative prophylaxis. Eighteen of 22 major procedures (82%; including 13 arthroplasties) were managed with additional hemostatic treatment: postoperative bleeding was observed in 12 (67%; 10 arthroplasties) of which six (33%) were treated (all arthroplasties). All procedures were managed with rFVIIa +/- tranexamic acid without any thrombotic complication.[32]

Surgical experience in patients on emicizumab out of clinical trials is being increasingly reported in form of either case reports[34,37–39,41,43–46,64–65] or case series.[33,40,42,47] Table 2 summarizes the real-world experience reported so far in form of case reports.

In the series described by Zimowski et al., seven procedures in patients with inhibitors were described: minor procedures were completed with observation alone and the remaining were successfully managed with standard doses of rFVIIa (90 mcg/kg). Two patients experienced mild postoperative bleeding complications both managed with a single rFVIIa bolus.[33] McCary et al. reported on 28 minor (21 port removals) and two major procedures in the frame of a US multicentre observational study on patients with and without inhibitors on emicizumab prophylaxis. Of the 21 port removals, 16 (76%) were performed with preoperative rFVIIa or FVIII treatment and two of them had treated postoperative bleeding which occurred in only one case among those performed without preoperative factor treatment. Both major procedures had been performed in noninhibitor patients who received FVIII concentrates for up to 1 week postoperatively to maintain FVIII levels above 50%.[40]

Another single-centre US experience including 20 minor and five major surgeries has been recently published.[42] In this series 9/20 (45%) minor procedures were planned to occur without any additional haemostatic support (including eight port removal) and bleeding complications occurred in four of them (44%; three port removal) as in three out of 11 (27%) pretreated minor procedures.

Indeed, port removal represents a common surgical procedure described in patients undergoing emicizumab prophylaxis. Swan et al. recently reported on 10 children (1 with current inhibitors) with severe HA who underwent port removal without any planned preprocedural prophylactic factor administration. All patients were discharged the day after surgery and no patient required any additional haemostatic therapy except one, who received oral tranexamic acid for five postoperative days due to minor bleeding from the surgical site.[47] Similar outcomes have been reported for a total of additional 27 CVAD removals included in the description of other case series on emicizumab use.[66–69] Of these only five received preoperative treatment[66] and only one experienced a mild postoperative bleeding.[68]

### 3.3 | Perioperative management of PWH treated with fitusiran

Fitusiran is an investigational small interference RNA developed to suppress antithrombin (AT) synthesis in hepatocytes to rebalance haemostasis in patients with HA or HB with and without inhibitors.[70] In the phase 3 study, monthly subcutaneous injections of fitusiran led to a durable, dose dependent AT reduction with improved thrombin generation and decreased bleeding frequency.[71]

During Phase 2 studies a fatal cerebral sinus vein thrombosis occurred in a noninhibitor PWHA following standard dose FVIII treatment for a breakthrough bleed and the program was put transiently on hold until the development of a risk-mitigation strategy with protocol guidelines on the use of low doses of FVIII/FIX and BPAs to treat breakthrough bleeds. More recently, three additional nonfatal vascular thrombotic events occurred in the frame of the late phase 3 trials despite adherence to breakthrough bleed management guidelines and were attributed to AT levels reduced below 10%. As a result, the studies have been resumed targeting higher AT levels, seeking to maintain a favourable benefit-risk balance for patients.[72,73]

A preliminary report of eight major surgical procedures (two tooth extractions, four joint replacements [bilateral knee in one case], nasal septoplasty, thoracotomy plus lung segmentectomy, and cholecystectomy) done in seven patients receiving fitusiran in the phase 2 extension trial is available.[27] All patients had AT levels < 20%, and no thromboprophylaxis was administered. Perioperative haemostatic treatment (FVIII concentrates and/or BPA) was administered in 7/8 procedures (at reduced doses in 5). Neither thrombotic nor bleeding complications have been reported.

### 3.4 | Perioperative management of PWH treated with concizumab

Concizumab is a recombinant monoclonal antibody able to inhibit TFPI thus enhancing FX activation by FVII/TF complex. It is currently under investigation in phase 3 trials as a once-daily subcutaneous prophylaxis in patients with HA or HB with or without inhibitors. Phase 2 trials (explorer 4 and 5) consisted of a main and extension part with patients receiving concizumab at an initial dose of .15 mg/kg with the option to escalate to .20 and .25 mg/kg upon breakthrough bleeds occurrence.[74]

During phase 2 studies no thrombotic events occurred, whereas three nonfatal events were observed during the phase 3 clinical program which was put transiently on hold to put in place an adequate risk management plan and recently resumed.[75,76] Those events occurred during concomitant use of additional haemostatic agents to concizumab prophylaxis.

Minor surgery was permitted during phase 2 trials while major surgery was no allowed and constituted protocol deviation. To date, 17 and 33 minor surgeries have been performed in explorer 4 and 5 trials, respectively.[29] In explorer 4 all patients (but one) were on .15 mg/kg concizumab at time of surgery, while in explorer 5 some procedures were performed in patients on .20 or .25 mg/kg concizumab; a total of six (one severe) and nine surgery-related bleeds were observed in either trial, respectively.[29]

### 3.5 | Laboratory monitoring

The availability of reliable laboratory assays to assess haemostasis during nonfactor replacement therapy is a requirement for the management of severe breakthrough bleeds and major surgery. In these settings, FVIII monitoring is often required during replacement therapy. Inhibitor testing is also needed, particularly to guide the therapeutic decision of using BPAs or FVIII products. Furthermore, in these

**TABLE 2** Case reports of surgical experience of emicizumab

| Type of report | Patient | Surgery type | Perioperative treatment | Bleeding complications | References |
|---|---|---|---|---|---|
| Case report | 54-year-old male with high-titre inhibitors | Total hip replacement | rFVIIa (180 mcg/kg preop + 90 mcg/kg every 3 h on day 1–3, every 6 h on day 4–7, every 8 h on day 8–11 and every 12 h on day 12–14) | No | Seaman et al. (2019) |
| Case report | 72-year-old male with low-titre inhibitor (HR) | Osteosynthesis for humeral fracture | rFVIII-Fc 150 IU/kg preop bolus followed by continuous infusion at 4 IU/kg/h | No | Okamoto et al. (2019) |
| Case report | 23-year-old male with low-titre inhibitor | Open reduction and internal femoral fixation | rFVIIa 90 mcg/kg perop and every 2 h<br>FVIII 100 IU/kg every 8 h as rescue treatment tapered over 10 days | Yes, hip hematoma | Chou et al. (2019) |
| Case report | 60-year-old male with low-titre inhibitor (HR)<br>60-year-old male with high-titre inhibitor | Total hip replacement<br>Total bilateral ankle replacement | pdFVIII 100 IU/kg preop + every 8 h until day 5<br>rFVIIa 90 mcg/kg every 2 h for 48 h followed by 90 mcg/kg every 3 h until day 7 | No<br>No | Biron-Andreani et al. (2020) |
| Case report | 48-year-old male with high-titre inhibitor | Removal of femoral spacer<br>Reimplantation of knee replacement | rFVIIa 90 mcg/kg preop + 90 mcg/kg after 2 h followed by 50 mcg/kg/h continuous infusion on day 1–4, 25 mcg/kg/h on day 5 and 90 mcg/kg every 3 and 6 h on day 6 and 7<br>rFVIIa 90 mcg/kg every 2 h up to 3 doses followed by 50 mcg/kg/h continuous infusion on day 2–5*, 25 mcg/kg/h on day 6–11, 75 mcg/kg every 4 and 6 h on day 12 and 13 | No<br>Yes, *rescued by 8 rFVIIa 90 mcg/kg boluses every 2 h on day 1 | Evans et al. (2020) |
| Case report | 57-year-old male without inhibitor | CABG | rFVIII 50 IU/kg bolus postoperatively followed by 2 IU/kg/h continuous infusion for 5 days and twice-daily boluses for additional 5 days | No | Isaacs et al. (2020) |
| Case report | 50-year-old-male with high-titre inhibitor | Internal fixation for fracture | rFVIIa 94 mcg/kg + tranexamic acid preop followed by 82 mcg/kg every 3 h | No | Anzej Doma et al. (2020) |
| Case report | 14-year-old male with high-titre inhibitor | Arthroscopic synovectomy | rFVIIa 80 mcg/kg preop and every 3 h on day 1, every 4 h on day 2, and every 6 h on day 3 | No | Mizumachi et al. (2021) |
| Case report | 14-year-old male with high-titre inhibitor<br>15-year-old male with high-titre inhibitor | CVAD removal<br>CVAD removal | rFVIIa 45 mcg/kg preop only<br>rFVIIa 90 mcg/kg preop only | No<br>No | Lockhart et al. (2021) |
| Case report | 9-year-old male with low-titre inhibitor (HR) | Femoral varization osteotomy | rFVIII-Fc 150 IU/kg preop bolus followed by 12 IU/kg/h continuous infusion until day 6.<br>From day 6 rFVIIa 90 mcg/kg every 8–10 h | No | Lefèvre et al. (2021) |
| Case report | 44-year-old male without inhibitor | Total elbow replacement | rFVIII 4000 IU preop bolus followed by 4 IU/kg/h continuous infusion until day 5 | No | Guillaume et al. (2021) |

conditions, laboratory monitoring may be helpful for early detection of prothrombotic markers in patients treated with FVIII/FIX or BPAs.

It is important to be aware that emicizumab interferes with all aPTT-based assays and, therefore, neither the inhibitor titre nor the FVIII activity should be measured using the conventional clotting assays. Suitable solutions are to assess the inhibitor titre or FVIII activity by chromogenic assays employing bovine reagents that are insensitive to emicizumab.[77] According to the mechanism of action of fitusiran or concizumab, it appears possible to measure FVIII activity and inhibitor titre using the conventional aPTT-based assays in the presence of these therapeutic agents.

## CONFLICTS OF INTEREST

Maria Elisa Mancuso has received honoraria as consultant/advisor or speaker from Bayer, Biomarin, CSL Behring, Catalyst Bioscience, Grifols, Kedrion, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Sobi, Spark Therapeutics, Takeda, UniQure. Cedric Hermans has received honoraria as consultant or speaker from Bayer, Takeda, SOBI, Octapharma, CSL-Behring, Pfizer, Roche, Grifols, Kedrion, Novo Nordisk, LFB, Spark, Biomarin.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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