Continuous infusion of recombinant activated factor VII: a review of data in congenital hemophilia with inhibitors and congenital factor VII deficiency

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Introduction: Continuous infusion (CI) of clotting factors as a replacement therapy for perioperative hemostatic protection has been performed for many years, including with factors VIII and IX and recombinant activated factor VII (rFVIIa). This approach provides steady factor levels without requiring frequent administration of bolus doses.

Aim: To review safety, efficacy, and dosing data regarding CI of rFVIIa for hemostatic management of patients with congenital hemophilia with inhibitors (CHwI) or congenital factor VII deficiency (C7D).

Materials and methods: A literature review identified instances of CI of rFVIIa in patients with CHwI or C7D undergoing surgery or experiencing bleeding episodes. Data regarding safety, efficacy, and dosing were extracted.

Results: The safety and efficacy of 50 mcg/kg/h CI of rFVIIa following a 90 mcg/kg bolus injection, vs a standard bolus injection regimen, was reported for 24 patients with CHwI undergoing elective surgery in an open-label, randomized, Phase III trial. Efficacy was similar between CI and bolus injection groups at all postoperative time points assessed. Additionally, a postmarketing surveillance study reported effective (80%) and partially effective (20%) CI of rFVIIa in a Japanese cohort of ten patients with CHwI who underwent 15 surgical procedures. Finally, the safety and dosing of rFVIIa CI in 193 and 26 patients with CHwI and C7D, respectively, were reported in 11 prospective studies, 10 retrospective studies, and 30 case reports. No unexpected safety findings were reported.

Conclusion: rFVIIa CI has been performed safely and effectively in patients with CHwI and C7D undergoing surgery and during bleeding episodes in patients with CHwI.

Keywords: rFVIIa, continuous infusion, surgery, bleeding

Introduction
Continuous infusion (CI) of replacement clotting factor VIII (FVIII) and factor IX (FIX) has been performed for many years in the context of perioperative management of bleeding, and provides a means of ensuring continuous factor activity at a steady level without requiring frequent nursing administration of small bolus doses.1,2 After this approach was initially suggested by Brinkhous in the early 1950s,3 experience with CI has accumulated in situations requiring intensive FVIII replacement.4-8 More recently, interest in this administration approach has been supported by improvements in the stability of newer factor concentrates and the ability to achieve stable hemostatic effect with substantial factor savings (estimated as 20%-50%).9
Advantages of CI are reflected in the current World Federation of Hemophilia guidelines, which include the use of purified FIX as well as FVIII concentrates and state that “continuous infusion avoids peaks and troughs and is considered by some to be advantageous and more convenient.”

Furthermore, these guidelines state that the use of CI may reduce the amount of clotting factor concentrates administered, and therefore may be cost-effective, particularly in patients with severe hemophilia. Evidence supporting the World Federation of Hemophilia guidelines for CI of FVIII and FIX comes from several studies demonstrating that CI provided similar efficacy to bolus injections (BIs) with higher nadir factor levels and lower drops in hemoglobin and blood transfusion requirements, and reduced overall factor use.

Recombinant activated coagulation factor VII (rFVIIa; NovoSeven® RT; Novo Nordisk A/S, Bagsværd, Denmark) is a highly purified recombinant protein, the development of which began clinically with compassionate/emergency use programs initiated in 1998 and continued through multiple formal clinical studies that were conducted in the subsequent 15–20 years in both the treatment of bleeding and perioperative management settings. The product is approved by the US Food and Drug Administration for the treatment of bleeding episodes and the prevention of bleeding in surgical interventions or invasive procedures in patients with hemophilia A or B with inhibitors, congenital FVII deficiency (C7D), and Glanzmann’s thrombasthenia (GT) with refractoriness to platelets with or without antibodies. It is also indicated for the treatment of bleeding episodes and the prevention of bleeding in surgical interventions or invasive procedures in adults with acquired hemophilia (AH).

Although currently indicated in the US for BI only, several early studies document the use of rFVIIa administered by CI. Following an initial dose-finding study that randomized patients to two rFVIIa doses for perioperative management, interest was generated in specifically comparing rFVIIa BI and CI approaches to surgery based on early published experiences with rFVIIa. One study specifically reported reduced rFVIIa utilization of CI compared with BI and a reduction in nursing care required for severe bleeding and perioperative management. This led to the first randomized trial comparing BI with CI of bypassing agents for perioperative management. In parallel with the clinical studies, registries continue to capture CI data, and multiple case reports and series have documented successful CI of rFVIIa for perioperative management of patients with congenital hemophilia with inhibitors (CHwI) or C7D. This literature review presents the clinical experience of patients with CHwI and C7D who were treated with rFVIIa CI. Together, the studies reviewed evaluate the safety and efficacy of rFVIIa CI in these patient populations.

Materials and methods

A systematic literature review was conducted to identify patients treated with rFVIIa CI between January 1, 1995 and September 30, 2016 using ProQuest and InsightMeme. Included articles were published in English and were required to present some data from patients with CHwI or C7D, even if other indicated uses of rFVIIa (ie, AH or GT) were also presented. Articles reporting data exclusive to other indications were excluded. This analysis presents all information available from all publications identified, without attempting to remove any potential duplicate reporting; however, in cases of newer publications that clearly referred to being inclusive of previously reported results, only the updated results were used.

The following search terms were used: (h*emophilia AND inhibitor*) AND (continuous NEAR/3 (infuse OR infusing OR infusion)) AND (novoseven OR rfvii OR “recombinant factor viia” OR “recombinant coagulation factor vii” OR “recombinant activated factor vii” OR “eptacog alfa”) and “factor VII deficien*” AND (continuous NEAR/3 (infuse OR infusing OR infusion)) AND (novoseven OR rfvii OR “recombinant factor viia” OR “recombinant coagulation factor vii” OR “recombinant activated factor vii” OR “eptacog alfa”). Safety, efficacy, and dosing data were extracted from the reports identified, where available.

Results

The literature search captured a total of 241 patients who experienced 453 bleeding episodes, 223 surgical procedures, and 46 unspecified episodes (bleeds/surgeries) in which rFVIIa CI was used as part of the treatment regimen.

In the context of CHwI, 45 published references were identified. Of these, one reference described a randomized parallel trial (BI vs CI) and one a postmarketing surveillance study. In addition, 9 prospective studies, 9 retrospective studies, 7 case series reporting on two or more patients, and 18 case reports on a single patient were identified. Together, these references included 215 patients treated for 453 bleeding episodes, 177 surgeries or procedures, and 46 unspecified episodes (bleeds/surgeries). Of note, information specific to eleven patients with AH and two patients with GT could not easily be removed, and therefore, it is included in the overall population consisting primarily of patients with CHwI.
In the context of C7D, eight published references were identified. These references included two prospective studies, one retrospective study, one case series reporting on two or more patients, and four case reports on a single patient. Data were captured for 26 patients with C7D who were administered rFVIIa CI for a total of 46 surgeries.

Direct comparison of CI to BI of rFVIIa in patients with CHwI: pivotal open-label study

Due to interest in comparing the safety and efficacy of CI vs BI of rFVIIa, Novo Nordisk conducted an open-label, randomized, parallel trial comparing CI (n=12) and intravenous BI (n=12) of rFVIIa in patients with hemophilia A or B with inhibitors who were undergoing elective major surgery.16,23 The types of surgeries performed included knee (n=2), hip (n=2), abdomen/lower pelvis (n=2), groin/inguinal (n=2), circumcision (n=1), eye (n=1), frontal/temporal region of cranium (n=1), and oral cavity (n=1).

Overall dosing regimens for each treatment group are shown in Figure 1. Prior to surgery, a 90 mcg/kg bolus dose of rFVIIa was administered to patients in each group; the BI group then received 90 mcg/kg rFVIIa every 2 hours during the procedure and for the first 5 days, then every 4 hours from days 6–10. The CI group received 50 mcg/kg/h rFVIIa during the procedure and for the first 5 days, followed by 25 mcg/kg/h from days 6–10. For both rFVIIa-treated groups, two bolus rescue doses (90 mcg/kg) were permitted during any 24-hour period.

Efficacy assessments at each time point for both treatment groups are summarized in Table 1. The BI and CI treatment groups showed comparable efficacy in achieving and maintaining hemostasis in major surgery from wound closure through day 10. At 24 hours after surgery, treatment was rated as effective in 12 of 12 patients (100%) in the bolus treatment group and in 10 of 12 patients (83.3%) in the CI treatment group, and at postoperative day 10 was effective in 9 of 12 patients (75.0%) in the bolus treatment group and in 10 of 12 patients (83.3%) in the CI treatment group. Median days of rFVIIa dosing, median numbers of additional BI, and mean total doses were similar between the BI and CI groups (Table 2). The mean total doses of rFVIIa administered were 237.5 mg (BI) and 292.2 mg (CI).

Of the 24 total patients, 7 had serious adverse events (SAEs; 4 in the BI group and 3 in the CI group). Four of these SAEs were considered probably or possibly related to rFVIIa treatment (two events of decreased therapeutic response in each treatment arm). No deaths occurred during the study period.

Postmarketing surveillance study in patients with CHwI

A postmarketing surveillance study was performed to assess the safety and hemostatic efficacy of rFVIIa administered as a BI and/or by CI.24 The study included 37 Japanese patients with congenital hemophilia A or B with inhibitors (n=32) or AH (n=5) undergoing a total of 66 surgical procedures. CI administered after an initial BI of rFVIIa was used in 15 major or minor procedures in ten patients with congenital hemophilia A or B with inhibitors.

Postoperative bleeding control was rated effective or slightly effective in all patients with CHwI who received rFVIIa CI (Table 3). CI dosing of rFVIIa ranged from 8–60 mcg/kg/h over a duration of 5–16 days. Local thrombophlebitis was reported in one patient who received concomitant immune tolerance induction with recombinant FVIII.

Additional prospective studies, retrospective studies, and case reports in patients with CHwI

In addition to the open-label study and the postmarketing surveillance study, the literature review identified 43 relevant publications containing information on 193 patients with
CHwI (including 11 patients with AH and 2 patients with GT) who experienced 649 bleeding episodes and surgical procedures that were treated with rFVIIa CI. These references included 9 reports of prospective series with 84 patients treated for 392 bleeding episodes, 55 surgeries, and 46 bleeds/surgeries; 9 reports of retrospective series with 64 patients treated for 39 bleeding episodes and 64 surgeries; and 25 case reports/series detailing 45 patients treated for 22 bleeding episodes and 31 surgeries.

CI dosing characteristics and adverse events (AEs) possibly or probably related to rFVIIa in patients with CHwI are summarized in Table 4; of note, efficacy was not formally assessed in all these studies. CI dosing in patients with CHwI ranged from 2.5–120.0 mcg/kg/h, and duration of CI dosing ranged from 4 hours to 34 days. Of the 193 patients with CHwI, a total of 38 adverse drug reactions (ADRs) possibly or probably related to administration of rFVIIa were reported in 19 patients, including wound infection or device-related sepsis (6), hemorrhosis (7), and procedural or postprocedural hemorrhage (8).

### Prospective studies, retrospective studies, and case reports in patients with C7D

In the context of C7D, the literature search returned eight relevant publications reporting data from 26 patients who underwent 46 major and minor surgeries and were treated with rFVIIa CI. These references include two prospective studies with 13 patients undergoing 28 surgeries, one retrospective study with 7 patients undergoing 12 surgeries, and 5 case reports/series of 6 patients undergoing 6 surgeries.

CI dosing characteristics and AEs possibly or probably related to rFVIIa in patients with C7D are summarized in Table 5; of note, efficacy was not formally evaluated in these publications. CI dosing of rFVIIa in patients with C7D who were undergoing surgery ranged from 0.2–30.0 mcg/kg/h, and duration of CI dosing ranged from 8 hours to 10 days. Of the 26 patients with C7D, one patient reported a total of two ADRs possibly or probably related to rFVIIa (major perioperative bleeding and development of transient rFVIIa inhibitors).

### Discussion

Perioperative CI of rFVIIa may be a useful alternative to BIs in some circumstances, and use of this administration method has been reported in various patient populations. Potential advantages of CI proposed initially by Schulman et al include the ability to provide patients with constant levels of rFVIIa, possible cost savings associated with the avoidance of peaks in rFVIIa levels based upon demonstrated lower utilization, and reduced administrative burden (hanging

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**Table 1** Open-label study – efficacy of bolus dosing vs continuous infusion in major surgery in patients with congenital hemophilia with inhibitors

| Parameter                        | Bolus injection (90 mcg/kg) (n=12) | Continuous infusion (50 mcg/kg/h) (n=12) |
|----------------------------------|-----------------------------------|---------------------------------------|
| Number of additional bolus doses | 0 (0–3)                           | 0 (0–4)                               |
| Mean total dose, mg              | 237.5                             | 292.2                                 |

**Notes:** Data from Pruthi et al. Patients who completed the study early, having achieved hemostasis, were counted as effective at subsequent time points. Patients who discontinued due to treatment failure were counted as ineffective at subsequent time points. Eight patients completed the study early because their bleeding had resolved. Four patients dropped out of the study due to ineffective therapy, and one patient left the study due to a hemorrhosis that was described as an adverse event. One of the patients randomized to the bolus injection arm had an autoimmune inhibitor to coagulation factor VIII and was included in the efficacy analysis.

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**Table 2** Open-label study – dosing by treatment group in patients with congenital hemophilia with inhibitors

| Parameter                        | Bolus injection (90 mcg/kg) (n=12) | Continuous infusion (50 mcg/kg/h) (n=12) |
|----------------------------------|-----------------------------------|---------------------------------------|
| Days of dosing, median (range)   | 10 (4–15)                        | 10 (2–116)                            |
| Number of bolus injections, median (range) | 38 (26–42) | 1.5 (0–7) |
| Number of additional bolus doses | 0 (0–3)                           | 0 (0–4)                               |
| Mean total dose, mg              | 237.5                             | 292.2                                 |

**Notes:** Data from Pruthi et al. Includes dosing during the follow-up period after the 10-day study period. For both recombinant activated factor VII-treated groups, two bolus rescue doses (90 mcg/kg) were permitted during any 24-hour period. Five patients in the bolus group and four patients in the continuous infusion group required additional bolus doses.
one infusion bag a day) compared with regular bolus dosing every two or three hours during surgery and until hemostasis or healing has occurred. As noted by Pruthi et al, the planned dosage schedule precluded direct comparison of the required rFVIIa dose of CI vs BI. Previous investigation demonstrated the biochemical stability and maintenance of sterility of rFVIIa over 24 hours of CI when kept at room temperature, supporting the ability to infuse a constant dose over time. Our analysis aimed to summarize available temperature, supporting the ability to infuse a constant dose of CI for 24 hours of CI when kept at room temperature, demonstrating the biochemical stability and maintenance of sterility of rFVIIa.

### Table 3: Postmarketing surveillance study – dosing and efficacy of continuous infusion of rFVIIa in patients with congenital hemophilia with inhibitors

| Patient | Age, years | Type of surgery | Total dose, mcg/kg | Dosing regimen | Continuous infusion, mcg/kg/h | Treatment duration, days | Postoperative control |
|---------|------------|----------------|-------------------|----------------|-----------------------------|--------------------------|-----------------------|
| **Hemophilia A** | | | | | | | |
| 1 | 32 | Shoulders arthroplasty | 1,830 | 92 | 14–28 | 5 | Effective |
| 3 | 11 | Elbow arthroplasty | 5,930 | 60–100 | 10–30 | 6 | Effective |
| 16 | 20 | Arthroscopic synovectomy (knee) | 5,470 | q2 hours ×12 | 15–30 | 6 | Effective |
| 18 | 7 | Arthroscopic synovectomy (knee) | 1,690 | 100 | 17–26 | 3 | Effective |
| **Hemophilia B** | | | | | | | |
| 7 | 36 | Arthroscopic synovectomy (knee) | 3,680 | 102 q2 hours ×9 | 13–17 | 14 | Slightly effective |
| 8 | 12 | Arthroscopic synovectomy (knee) | 3,470 | 102 q2 hours ×12 | 26–34 | 6 | Effective |
| 9 | 15 | Femoral head replacement | 3,890 | 95 q2 hours ×12 | 14–29 | 7 | Effective |
| 17 | 36 | Arthroscopic synovectomy | 5,000 | 100 q2 hours ×16 | 13–33 | 15 | Slightly effective |

Notes: Data from Takedani et al. Continuous rFVIIa infusion was administered after bolus injection. Postoperative bleeding control (up to 3 days after surgery) was judged as effective (bleeding stopped or considerably reduced), slightly effective (bleeding slightly reduced), or not effective (bleeding not reduced). Treatment regimen included concomitant immune tolerance induction with recombinant factor VIII from the operative day. rFVIIa use before physiotherapy and for regular prophylaxis is included. Other bypassing agents were used in addition to rFVIIa.

### Congenital hemophilia with inhibitors

In the context of CHwI, identified reports included a pivotal randomized trial, a postmarketing surveillance study, and 43 additional prospective studies, retrospective studies, and case reports/series. In the pivotal trial, CI patients received a BI of 90 mcg/kg rFVIIa (consistent with recommended bolus dosing), followed by 50 mcg/kg/h CI; in other studies, CI dosing varied, ranging from 8–60 mcg/kg/h (postmarketing surveillance study) or 2.5–120 mcg/kg/h (additional reports).

Although efficacy was not formally evaluated in the small prospective/retrospective studies and case reports/series, the reported efficacy of rFVIIa CI in the pivotal trial and postmarketing surveillance study ranged from 80–83.3%, and rFVIIa CI was rated either as effective or partially effective in all 15 procedures (100%) in the postmarketing surveillance.
Table 4 Prospective studies, retrospective studies, and case reports – dosing and safety of continuous infusion of rFVIIa in patients with congenital hemophilia with inhibitors

| Reference | Select content | Continuous infusion dosing | Adverse drug reactions |
|-----------|----------------|----------------------------|-----------------------|
|           |                | Dose, mcg/kg/h | Duration | Previously failed/concurrent treatment |                          |
| Prospective studies |               |               |          |                                     |                          |
| Chuansumrit et al, 2000 | Two of five patients with CHwI (four HA, one HB) received rFVIIa for three acute bleeding episodes | 16.5 (individual dosing) | 64–202 hours | Tranexamic acid, packed red blood cells, fibrin glue, intravenous immunoglobulin | None |
| Kenet et al, 2000 | Six patients with CHwI (HA) received rFVIIa for 101 bleeding episodes with either regular dose protocol (R) or augmented dose protocol (A) | R: 15–16 ×12 hours A: 30 ×6 hours | R: 29–100 hours A: 9–18 hours | NR | None |
| Santagostino et al, 2001 | 28 patients with CHwI (25 HA) received rFVIIa for 31 episodes and 3 patients with AH received rFVIIa for 4 episodes. Overall, there were 10 spontaneous bleeding episodes, 11 major surgeries, and 14 minor surgeries | 10–50 | 1–34 days | Tranexamic acid, porcine FVIII, other FVIII, packed red blood cells | None |
| Smith et al, 2001 | Eight patients with CHwI (six HA) received rFVIIa for six major surgeries and two patients with AH received rFVIIa for two minor surgeries | 16.5 | 1–26 days | Platelets, cryoprecipitate | Device failure (1), hemarthrosis (1), therapeutic response decreased (1), extravasation (1), device-related sepsis (1), injection site thrombosis (2), postprocedural hemorrhage (3), postoperative wound infection (4), procedural hemorrhage (4) |
| Mauser-Bunschoten et al, 2002 | Ten patients with CHwI (eight HA, two HB) received rFVIIa for 28 bleeds and seven surgeries, and four patients with AH received rFVIIa for six bleeds and two surgeries | 2.5–35 | 44 hours–12 days | Tranexamic acid | None |
| Ludlam et al, 2003 | Nine patients with CHwI (HA) received rFVIIa prior to nine elective major orthopedic surgeries | 50 | 7–20 days | Tranexamic acid | Incision site hemorrhage (1), thrombocytopenia (1), thrombophlebitis (1), anemia (1), wound infection (1), cellulitis (2), hemarthrosis (6) |
| Kenet et al, 2003 | Three patients with CHwI received rFVIIa under two continuous infusion treatment regimens (ClA, ClB) for 244 bleeding episodes | ClA: 15–16 ClB: 30 | 4–100 hours | NR | None |
| Takedani et al, 2010 | Three of seven patients with CHwI received rFVIIa for four orthopedic surgeries with bolus injection + continuous infusion | 16.5 | 3–7 days | Tranexamic acid | None |
| Ogura et al, 2011 | Six patients with CHwI received rFVIIa for 46 unspecified episodes (bleeds/surgeries) | 15–50 | 3–8 days | Tranexamic acid | None |
| Retrospective studies |               |               |          |                                     |                          |
| Schulman et al, 1998 | 28 patients with CHwI (25 HA, 3 HB), 2 patients with AH, and 2 patients with GT received rFVIIa for 29 bleeding episodes or 26 surgeries | NR | 1–16 days | Fresh frozen plasma, antithrombin, packed red blood cells, platelets, tranexamic acid, epsilon-aminocaproic acid | Thrombophlebitis (4) |
| Authors               | Patients Details                                                                 | Treatment Duration | Treatment Details                                                                 | Outcome |
|----------------------|----------------------------------------------------------------------------------|--------------------|-----------------------------------------------------------------------------------|---------|
| Mauser-Bunschoten et al, 1998[63] | Seven patients with CHwI received rFVIIa for four bleeding episodes and five surgeries | 6–30              | 1–14 days                                          | Tranexamic acid | None            |
| Ettingshausen et al, 1999[63] | Six patients with CHwI (HA) received rFVIIa for five surgeries and five bleeding episodes | 10–35             | 4–18 days                                          | Tranexamic acid, packed red blood cells | None            |
| Hebermann et al, 2004[63] | Four patients with CHwI (HA) received rFVIIa for six major elective orthopedic surgeries | 35–50             | ≥8 days                                            | FVII, tranexamic acid | None            |
| Solimeno et al, 2006[63] | Two of six patients with CHwI received rFVIIa for six major elective orthopedic surgeries | 16.5              | NR                                                | PCC                | Insufficient response (1) |
| Jenkins et al, 2013[63] | One of eight patients with CHwI received rFVIIa for total knee replacement surgeries | 50                | NR                                                | NR                | None            |
| Batorova et al, 2014[63] | One of seven patients with HA (six severe, one moderate, two with inhibitors) received rFVIIa for iliopsoas bleed | 3                 | 5 days                                            | PCC                | None            |
| Mancuso et al, 2014[63] | Patients with CHwI (HA) received rFVIIa for four major orthopedic procedures | 31                | NR                                                | Tranexamic acid, packed red blood cells | None            |
| Linari et al, 2015[63] | Eleven patients with CHwI received rFVIIa for 15 total knee replacement surgeries | 15–50             | 14 days                                           | Packed red blood cells, PCC | Pulmonary embolism (1) |

**Case reports/series**

| Authors | Patients Details                                                                 | Treatment Duration | Treatment Details                                                                 | Outcome |
|---------|----------------------------------------------------------------------------------|--------------------|-----------------------------------------------------------------------------------|---------|
| Gringeri et al, 1991[63] | One patient with CHwI (HA) received rFVIIa for inguinal hernioplasty surgery | 38                | 12 hours                                          | Porcine FVIII, tranexamic acid, packed red blood cells | None            |
| Hedner, 1991[63] | One patient with CHwI received rFVIIa for extensive herniotomy surgery | 38                | NR                                                | Porcine FVIII, tranexamic acid | None            |
| Schulman et al, 1996[63] | Two patients with CHwI (HA) received rFVIIa for four treatment episodes prior to elective surgery or traumatic procedure | 15.5–31           | 3.5–14 days                                       | Tranexamic acid, fibrin glue | None            |
| Stieltjes et al, 1997[63] | One patient with CHwI (HA) received rFVIIa for removal of osteosynthesis surgery | 20                | NR                                                | Porcine FVIII, anti-inhibitor coagulant complex | None            |
| Vermylen and Peerlinck, 1998[63] | Two patients with CHwI (HA) received rFVIIa for three surgeries | 6–29              | 13–14 days                                        | Tranexamic acid | None            |
| Menart et al, 1998[63] | One patient with CHwI (HA) received rFVIIa postoperatively after a total knee replacement surgery | 20                | 10 days                                           | pd-FVIII, other FVIII, cryoprecipitate | None            |
| Montoro et al, 1998[63] | One patient with CHwI (HA) received rFVIIa via minipump as prophylaxis during insertion of central venous catheter | 4.3–7.6           | 5 days                                            | Tranexamic acid | None            |
| Scaraggi et al, 1999[63] | One patient with CHwI (HA) received rFVIIa for severe iliopsoas hematoma | 4.7–16.7          | 17 days                                           | NR                | None            |
| Lorenzo et al, 1999[63] | One patient with CHwI (HA) received rFVIIa for open knee evacuation surgery | 20                | 7 days                                            | NR                | None            |
| Peerlinck and Vermylen, 1999[63] | One patient with CHwI (HA), aged 72 years, received rFVIIa for dental extraction surgery | 30                | NR                                                | Tranexamic acid, packed red blood cells | Acute myocardial infarction (1) |
| Baudo et al, 2000[63] | Four patients with CHwI (HA) received rFVIIa through a central vein catheter for two surgeries in one patient and three bleeding episodes in three patients | 11.5–20           | 4–18 days                                         | Porcine FVIII | None            |

(Continued)
### Table 4 (Continued)

| Reference                  | Select content                                                                                                                                                                                                 | Continuous infusion dosing*                                                                 | Adverse drug reactions*                                                                 |
|---------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Tagariello et al, 2000    | Two patients with CHwI (HA) received rFVIIa for two total hip replacement surgeries                                                                                                                         | Dose, mcg/kg/h: 11–42 Duration: 12–29 days Previously failed/concurrent treatment: Tranexamic acid, packed red blood cells | None                                                                                    |
| McPherson et al, 2000     | Six Australian patients with CHw or AH (three HA, one HB, two AH) received rFVIIa for seven bleeding episodes (includes patients with CHwI with one intracranial hemorrhage, one iliopsoas hemorrhage, two wrist hemorrhosis, one sublingual hematoma, and one patient with AH with compartment syndrome and hemorrhage) and three surgeries (two Australian patients with AH for one retroperitoneal bleed and one surgical debridement and skin grafting; one Thai patient with CHwI for one surgery) | Dose, mcg/kg/h: 10–49 Duration: 3–11 days Previously failed/concurrent treatment: Epsilon-aminocaproic acid, tranexamic acid, pd-FVIII | None                                                                                    |
| Faradji et al, 2001       | One patient with CHwI (HA) received rFVIIa for knee joint arthroplasty surgery                                                                                                                              | Dose, mcg/kg/h: 14–28 Duration: 14 days Previously failed/concurrent treatment: Packed red blood cells | None                                                                                    |
| Nakamura et al, 2002      | One patient with CHwI (HA) received rFVIIa for left elbow arthroplasty surgery                                                                                                                                | Dose, mcg/kg/h: 10–30 Duration: 6 days Previously failed/concurrent treatment: Tranexamic acid | None                                                                                    |
| Perez et al, 2002         | One patient with CHwI (HA) received rFVIIa for hip arthroplasty surgery                                                                                                                                       | Dose, mcg/kg/h: 7–15 Duration: 12 days Previously failed/concurrent treatment: Tranexamic acid | None                                                                                    |
| Tagariello et al, 2002    | Six patients with CHwI received rFVIIa for seven major hemorrhages and two surgeries                                                                                                                       | Dose, mcg/kg/h: 100–120 Duration: 7–8 days Previously failed/concurrent treatment: NR         | None                                                                                    |
| Divanon et al, 2002       | Two of five patients with CHwI received rFVIIa for gastrointestinal bleeding or cholecystectomy                                                                                                           | Dose, mcg/kg/h: 10–30 Duration: 9–10 days Previously failed/concurrent treatment: PCC, packed red blood cells, tranexamic acid, FVII | None                                                                                    |
| Tagariello et al, 2003    | One patient with CHwI (HA) received rFVIIa during concurrent total hip replacement and total knee replacement surgery                                                                                     | Dose, mcg/kg/h: 21–40 Duration: 13 days Previously failed/concurrent treatment: Tranexamic acid | None                                                                                    |
| Hayashi et al, 2004       | One patient with CHwI (HA) received rFVIIa for serious retroperitoneal hematoma                                                                                                                              | Dose, mcg/kg/h: 30–40 Duration: 7–10 days Previously failed/concurrent treatment: PCC, packed red blood cells | None                                                                                    |
| Slaoui et al, 2004        | One of five patients with CHwI (HA) received rFVIIa before intestinal surgery                                                                                                                              | Dose, mcg/kg/h: NR Duration: 9 days Previously failed/concurrent treatment: Tranexamic acid | None                                                                                    |
| Margit et al, 2004        | One patient with CHwI (HA) received rFVIIa for major surgery                                                                                                                                               | Dose, mcg/kg/h: 18–29 Duration: 24 hours Previously failed/concurrent treatment: Tranexamic acid | None                                                                                    |
| Horvathova et al, 2004    | One patient with CHwI received rFVIIa for hematuria and kidney hematoma                                                                                                                                     | Dose, mcg/kg/h: 9–15 Duration: 7 days Previously failed/concurrent treatment: NR               | None                                                                                    |
| Sartori et al, 2008       | One patient with CHwI (HA) received rFVIIa for bleeding episode                                                                                                                                             | Dose, mcg/kg/h: 14–30 Duration: 13 days Previously failed/concurrent treatment: Packed red blood cells, tranexamic acid | None                                                                                    |
| Candidotto et al, 2015    | One patient with CHwI (HA) received rFVIIa for replacement of infected knee prosthesis surgery                                                                                                              | Dose, mcg/kg/h: 25–40 Duration: 12 days Previously failed/concurrent treatment: pd-FVIII    | None                                                                                    |

**Notes:** *Single bolus doses (18.5–180 mcg/kg) may have been given to patients before and after continuous infusion with rFVIIa at the discretion of investigator or treating physician. Only adverse reactions possibly or probably related to rFVIIa treatment are provided. Bleeding episodes and surgeries are not separated by diagnosis.*

**Abbreviations:** AH, acquired hemophilia; CHwI, congenital hemophilia with inhibitors; FVIII, coagulation factor VIII; GT, Glanzmann’s thrombasthenia; HA, hemophilia A; HB, hemophilia B; NR, not reported; PCC, prothrombin complex concentrate; pd, plasma derived; rFVIIa, recombinant activated factor VII.
Table 5  
Prospective studies, retrospective studies, and case reports – dosing and safety of continuous infusion of rFVIIa in patients with congenital factor VII deficiency

| Reference | Select content | Continuous infusion dosinga | Adverse drug reactionsb |
|-----------|----------------|---------------------------|------------------------|
| Tran et al., 2011 | 64 | Ten patients with severe C7D received rFVIIa for 13 major and 12 minor surgeries | | Major perioperative bleeding (1), transient rFVIIa inhibitors (1) |
| Mariani et al., 2011 | 65 | 3 of 34 patients with C7D received rFVIIa for two major surgeries and one minor surgery | | None |
| Schulman et al., 2005 | 66 | Seven patients with C7D received rFVIIa for 12 elective surgeries | | None |
| Jiménez-Yuste et al., 2000 | 67 | One pregnant patient with moderate C7D received rFVIIa during cesarean section delivery | | None |
| Katori et al., 2008 | 68 | Two pediatric patients with C7D received rFVIIa for cardiac surgery after cardiopulmonary bypass termination | | None |
| Nagao et al., 2014 | 69 | One patient with severe C7D received rFVIIa for left total hip replacement surgery | | None |
| Rajpurkar et al., 2014 | 70 | One patient with severe C7D received rFVIIa for intracranial surgery | | None |
| Miyata et al., 2016 | 71 | One patient with asymptomatic C7D received rFVIIa for a right middle and lower lobectomy | | None |

Notes: Single bolus doses of 5-66 mcg/kg may have been given to patients before and after continuous infusion with rFVIIa at the discretion of the investigator or treating physician. Only adverse events possibly or probably related to rFVIIa treatment are provided.

Abbreviations: C7D, congenital factor VII deficiency; NR, not reported; PCC, prothrombin complex concentrate; rFVIIa, recombinant activated factor VII.

Table 6  
Summary of continuous infusion-treated events in patients with congenital hemophilia with inhibitors and congenital factor VII deficiency

| Congenital hemophilia with inhibitors | Congenital factor VII deficiency | Total |
|-------------------------------------|---------------------------------|-------|
| No. of patients | No. of episodes or procedures | No. of patients | No. of episodes or procedures |
| Clinical trial | Prospective reports | Retrospective reports | Case reports and series |
| 12 | 12 surgeries | NR | NR |
| Post-approval study | 10 | NR | NR |
| Prospective reports | 84 (includes 9 AH) | 392 bleeds | 55 surgeries |
| Retrospective reports | 64 (includes 2 AH, 2 GT) | 39 bleeds | 12 surgeries |
| Case reports and series | 45 | 71 | 12 surgeries |

Abbreviations: AH, acquired hemophilia; GT, Glanzmann's thrombasthenia; NR, not reported.
study. This generally high rate of efficacy is comparable to that observed with BIs in the only randomized parallel trial directly comparing these routes of administration\textsuperscript{23} and is also consistent with that previously reported for rFVIIa BI in registration trials (ie, 71\%–93\%),\textsuperscript{73–76} suggesting that no reduction in hemostatic efficacy occurs when rFVIIa is administered via CI vs BI.

Safety information was also extracted from all available CHwI reports. The most common SAEs previously reported with BI of rFVIIa in patients with CHwI in clinical trials and patient registries included thrombosis and decreased therapeutic response.\textsuperscript{16,18,77} Accumulated data from clinical trials and postmarketing studies found 13\% of AEs in patients with CHwI to be thrombotic events, the majority of which (60.3\%) recovered without sequelae.\textsuperscript{78} Of the total 215 patients with CHwI identified in the current analysis who experienced 676 bleeding episodes or surgical procedures, 43 ADRs possibly or probably related to administration of rFVIIa were reported. These included four ADRs reported in the pivotal trial (all decreased therapeutic response, with equal numbers occurring in each treatment arm) and one local thrombophlebitis reported in the postmarketing surveillance study. This safety profile of rFVIIa CI for perioperative management is, therefore, largely consistent with and supported by previous reports of rFVIIa BI use in patients with CHwI, and suggests the absence of any new safety signals associated with the CI route of administration.

**Congenital factor VII deficiency**

Compared with CHwI, fewer records of rFVIIa CI in patients with C7D were identified, with reports including eight prospective studies, retrospective studies, and case reports/series, together presenting data from 26 patients who underwent 46 surgical procedures. Reported dosing in these studies was in the range of 0.2–30.0 mcg/kg/h, which was lower than that observed for patients with CHwI, but consistent with a rate derived from dividing the recommended bolus dosing of 15–30 mcg/kg by the recommended 4–6-hour dosing interval.\textsuperscript{16} Lower rFVIIa dosing recommendations for factor replacement in C7D compared with use as a bypassing agent in CHwI are indicated in the current US prescribing information, with effective treatment for C7D reported with bolus dosing as low as 10 mcg/kg. Of note, the difference in mechanism of action of rFVIIa in these two disease states may account for differences in bolus dosing requirements, as supraphysiological FVIIa levels may be necessary to initiate bypassing activity in patients with CHwI and to achieve comparable efficacy to that seen in patients with C7D.\textsuperscript{79} The safety profile of rFVIIa CI in patients with C7D was generally consistent with that observed in patients with CHwI; of the 26 total patients identified with C7D, two ADRs in one patient possibly or probably related to rFVIIa administration were reported. While inhibitors to FVII replacement have been reported in patients with C7D receiving plasma and recombinant replacement, only one patient was noted to have transient inhibitory activity resulting in temporary dose adjustment in a case series of CI.\textsuperscript{64}

**Other considerations**

While not specifically evaluated or reported consistently in the literature, any use of rFVIIa by bolus or CI in the hospital setting needs to consider the severity or extensiveness of the bleed or surgical procedure and the need for coverage of postoperative physical therapy or rehabilitation. According to the prescribing information and based upon clinical studies, dosing was based upon weight and not upon age or body mass index. Although the limited amount of data comparing outcomes associated with CI vs bolus infusion limits our ability to recommend a CI dosing regimen, data from the pivotal open-label study in patients with CHwI support the effectiveness of a regimen including a 90 mcg/kg BI followed by 50 mcg/kg/h CI.\textsuperscript{23} Furthermore, an optimal dosing regimen in the context of C7D would likely include bolus dosing to achieve the desired FVIIa level for a particular procedure (eg, 15–30 mcg/kg as recommended in the prescribing information) followed by CI to maintain this level. Overall, the lack of any new safety signals associated with intensive rFVIIa treatment via CI, especially severe thrombotic events, is a key finding of our analysis and may be important in informing the potential use of this type of treatment.

Use of antifibrinolytics with rFVIIa has been described in many previous studies, although specific impact on the efficacy of rFVIIa has not been systematically studied. Antifibrinolytic use has not been reported to have an impact on the risk of thrombotic events. As noted in Tables 4 and 5, this is a common concurrent medication used for surgery in patients with CHwI and C7D, and not clearly associated with a difference in thrombotic risk in this review. Superficial thrombophlebitis in a peripheral vein used for CI is noted in this review in several cases, including the case series in which antifibrinolytics have been used, and the use of undiluted rFVIIa was noted as being a causative factor, not antifibrinolytics. One report does describe a 72-year-old hypertensive smoker who developed an acute myocardial event following a dental surgery where tranexamic acid 1,000 mg intravenous was administered preoperatively.\textsuperscript{47}
The recent development of new non-factor therapeutics for patients with CHwI (eg, emicizumab, fitusiran, concizumab) also raises new challenges in prescribing concomitant rFVIIa, and therefore, careful evaluation and monitoring of the safety and effectiveness of rFVIIa in this context should be performed.

Limitations
A key limitation to this analysis is the inconsistent use of concomitant hemostatic agents and highly variable dosing of rFVIIa for BI and CI across patients and reports, which complicates the interpretation of safety and efficacy assessments. Therefore, even though hemostatic management was achieved in many cases, efficacy may or may not be due solely to CI of rFVIIa, and direct comparisons cannot be made between studies. Additionally, inconsistent definitions of efficacy were used across reports, complicating the ability to draw conclusions across studies. However, these limitations are common in the context of rare diseases, which rely on real-world data, and our analysis benefited from systematically searching the published literature to obtain the maximum amount of patient data relevant to rFVIIa CI in populations of interest. We also cannot exclude the possibility that some reports may have included partially overlapping patient populations, and therefore, some individuals may have been included in our analysis more than once.

A key opportunity for future investigation may include performing a direct comparison between BI and CI of rFVIIa in patients with C7D, the absence of which complicates the ability to recommend therapeutic dose guidelines for CI administration in this patient population. This review also identified a combination of monitoring strategies including FVII activity to maintain a minimum target activity particularly in C7D and use of thrombelastography; although from this type of review, it is similarly difficult to identify the value in the monitoring strategies or specific target FVII:C ranges, and thrombelastography parameters were best described in the case of intracranial surgery.70

Conclusion
This review involved a systematic search of the published literature to identify reports of rFVIIa CI for hemostatic management in patients with CHwI or C7D, and it summarizes all available safety, efficacy, and dosing information. Efficacy of rFVIIa CI appeared to be high and comparable to that of BI, with reported ADRs consistent with the established safety profile of rFVIIa BI. CI may be a useful alternative to BIs for the perioperative management of bleeding in some patients with CHwI or C7D.

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