Recombinant factor VIIa: safety and efficacy

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Purpose of review

Recombinant factor VIIa has been increasingly used to provide hemostasis in nonapproved indications. This trend has resulted in concerns about safety, efficacy and costs.

Recent findings

Recombinant factor VIIa seems to have hemostatic effects in posttrauma and perisurgery excessive bleeding, although further studies are required. Recombinant factor VIIa may be used to reverse the effect of warfarin or other vitamin K-antagonist therapy following vitamin K administration. Some beneficial effects have also been suggested in a limited number of patients with liver disease and hemorrhagic stroke. Recombinant factor VIIa should be used with caution in cases with known hypercoagulability, excessive bleeding in the setting of disseminated intravascular coagulation or other states of generalized activation of the hemostatic system. In most of the nonapproved cases, a 4.8-mg vial administered to an adult patient weighing 50–100 kg to achieve a 50–100 μg/kg dose is recommended.

Summary

While consensus recommendations on the use of recombinant factor VIIa in nonapproved settings have been developed, more studies are needed to define dose and timing in these diverse patient populations. For now, decisions about off-label use of recombinant factor VIIa remain at the physician's discretion, assisted by hospital pharmacotherapeutic or transfusion committees.

Keywords

bleeding, efficacy, recombinant factor VIIa, safety

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Abbreviations

RBC red blood cell
rFVIIa recombinant factor VIIa

1065-6251

Introduction

Recombinant FVIIa (rFVIIa) has been approved for treatment of bleeding with inhibitors in patients with hemophilia. It has also been successfully used in non-hemophilia patients with acquired antibodies against factor VIII (acquired hemophilia). Pharmacological doses of rFVIIa have been found to enhance thrombin generation on activated platelets and, therefore, may also be of benefit in providing hemostasis in other (nonapproved) situations characterized by profuse bleeding and impaired thrombin generation [1], such as in patients with thrombocytopenia and in those with functional platelet defects [2,3]. Additionally, it has been used successfully in a variety of less-well-characterized surgical bleeding situations with dilutional and/or consumptive coagulopathies [4–6], as well as in patients with impaired liver function [7].

Because of the recent trends in rFVIIa usage in non-approved settings, significant concerns about its safety, efficacy, and costs have arisen. Additionally, dosing of rFVIIa for these potentially broad clinical applications is not standardized.

Experience with recombinant factor VIIa in nonapproved settings

To date, case reports, anecdotal experience, and limited clinical trials have largely described these uses; although data from randomized clinical trials have been limited [8], results of on-going trials have recently been published. Policies for the approval of rFVIIa therapy in non-approved settings should therefore undergo periodic review and revision as relevant new information and data are generated [9]; we review current evidence regarding safety and efficacy of rFVIIa therapy in nonapproved clinical settings.

Complex surgery and traumas resulting in profuse bleeding

A hemostatic effect has been demonstrated following the administration of rFVIIa in a limited number of patients after trauma and bleeding [5,6]. Seven trauma patients treated with rFVIIa after failure of conventional measures to achieve hemostasis [6] reported cessation of diffuse bleeding, and correction of abnormal coagulation assays; three of the seven patients died for reasons other than bleeding or from thromboembolism.

Anecdotal case reports have been published that describe the successful use of rFVIIa in patients with substantial

perisurgical bleeding [4]. The experience of rFVIIa use in trauma with excessive bleeding as well as in profuse postoperative bleeding, based largely on case reports, has indicated a hemostatic effect of rFVIIa given in doses of ranging from 20 to 120 μg/kg. The issue of preemptive, preoperative rFVIIa (40–90 μg/kg) was studied in nine patients with coagulopathy and urgent neurosurgical intervention [10]. Post-rFVIIa coagulation parameters normalized as early as 20 min after infusion, with no noted procedural or operative complications. No associated thromboembolic complications were observed. Subsequently, a prospective, randomized study of rFVIIa (20 or 40 μg/kg) compared with placebo perioperatively in 36 patients undergoing radical retropubic prostatectomy found that the cohorts receiving rFVIIa had substantially less median operative blood loss compared to the placebo group (1235, 1089, and 2688 ml, respectively) [11]. This study was not powered to demonstrate reductions in blood transfusions.

One study suggested that 'last-ditch' use of rFVIIa in patients with massive hemorrhage is ineffective, but this was an uncontrolled comparison between 10 patients treated with rFVIIa and 40 patients who were not [12]. In single-center series, 51 patients undergoing rFVIIa therapy for intractable blood loss after cardiac surgery were compared with 51 matched controls [13]. The authors found that bleeding 1 h after therapy was reduced in the treated cohort, compared with the control cohort. No differences in serious adverse events were noted. A subsequent review from the same institution of 114 cardiac surgery patients who received rFVII, compared with 541 concurrent patients who did not receive rFVIIa, concluded that rFVIIa is not associated with increased risk of adverse events, and early treatment may be associated with better outcomes [14]. A second series of rFVIIa in 53 patients during cardiac surgery found a significant decrease in doses of all blood products [15]. However, a third series of 24 patients treated with rFVIIa for refractory bleeding after cardiac surgery, compared with 24 matched controls, found no differences in red blood cells or plasma units transfused over a 24-h period [16].

Recently, a pilot study of 20 patients undergoing complex noncoronary cardiac surgery who were randomized to receive either placebo or rFVIIa (90 μg/kg) prophylactically after completion of cardiopulmonary bypass and reversal of heparin found a significantly reduced need for allogenic transfusion in the cohort who received rFVIIa [17]. However, a pediatric study of 76 pediatric patients undergoing surgery for congenital heart disease found no benefit of rFVIIa (40 μg/kg) prophylaxis as determined by chest closure time after cardiopulmonary bypass [18].

A randomized, placebo-controlled trial of rFVIIa as adjunctive therapy for control of bleeding in trauma patients was published recently [19]. In an analysis of 143 patients with blunt trauma, the percentage of patients alive at 48 h receiving more than 20 units of red blood cells (RBCs) was reduced from 33 to 14% ($P = 0.03$). For 143 patients with penetrating trauma, the reduction from 19 to 7% was not significant ($P = 0.08$). No differences in serious adverse events between the rFVIIa-treated and placebo cohorts were observed.

A retrospective registry database [20] of 40 patients with coagulopathic bleeding in a variety of medical and surgical settings (but excluding trauma) found an overall response rate of 80%, with no demonstrable differences among patients treated with <70 μg/kg, 70–90 μg/kg, or >90 μg/kg (Fig. 1). One or two administrations seemed to be enough to determine any effect on bleeding. Further controlled, randomized studies, however, are required to prove any beneficial effect of rFVIIa in these patients.

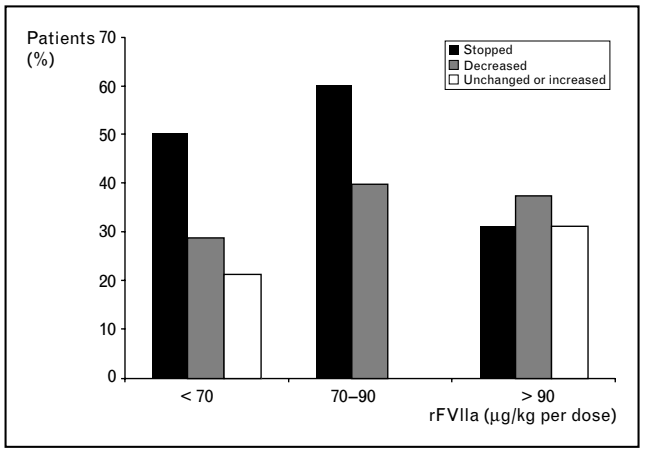
Congenital factor VII deficiency

In a randomized study, 17 factor VII-deficient patients were treated with rFVIIa [21], ranging from 21 to 27 μg/kg based on the dose capable of normalizing the prothrombin time 15 min after injection. The treatment resulted in excellent resolution of all hemarthroses treated. An infant with severe factor VII deficiency and massive intracranial hemorrhage was evaluated after administration of rFVIIa at three dose levels: 15, 22, and 30 μg/kg [22]. Factor VII levels were >100% between 30 and 180 min after each infusion, with mean trough levels above 25% at all three dose levels. Our recommended dosage for rFVIIa-replacement therapy in congenital factor VII deficiency is therefore 20 μg/kg (Table 1).

Patients receiving oral anticoagulant therapy

One report describes the use of rFVIIa in seven adult patients with prolonged international normalized ratio (or INR), three of whom required surgery. The doses administered ranged from 20 to 90 μg/kg, and all patients were reported to have a positive outcome [23]. These observations indicate that rFVIIa may be used to reverse the effect of warfarin or other vitamin K-antagonist therapy in cases in which the administration of vitamin K alone has been found to be insufficient. Two published reports of 15 total patients treated with rFVIIa for reversal of excessive anticoagulation with Coumadin support a dosage of 20 μg/kg, or 1.2 mg for an adult patient [24,25]. A recent review [26] of 12 patients with acute warfarin-associated intracranial hemorrhage over this same time period at one institution, all of whom received rFVIIa (30–135 μg/kg) as well as vitamin K (10 mg/day × 3) and fresh-frozen plasma (1307 ± 652 ml) for

Figure 1 Response to recombinant factor VIIa in each of three dose groups assessed by the treating clinician



Number of patients per group: <70 μg/kg per dose, $n = 14$; 70–90 μg/kg per dose, $n = 10$; >90 μg/kg per dose, $n = 16$. From [20] with permission from Blackwell Publishing.

treatment, found that treatment was associated with rapid correction of international normalized ratio; and that single doses appeared safe in this high-risk population [26].

Patients with impaired liver function

A hemostatic effect of rFVIIa has been proven in a limited number of liver disease patients [7]. In one clinical trial, 10 cirrhotic patients whose prothrombin time did not correct to within 2 s above the control reference value were given three successive doses of rFVIIa (5, 20, or 80 μg/kg) during a 3-week period in a randomized study [27]. The prothrombin time transiently corrected to normal in all three dosage groups.

A multicenter trial studied 71 patients with advanced liver disease who were undergoing laparoscopic liver biopsy [28]. The patients were randomized to receive one of four doses (5, 20, 80, or 120 μg/kg); 48 (74%) of 65 patients achieved hemostasis within 10 min. One thrombotic event and one case of disseminated intravascular coagulation were reported, but were not felt by the authors to be related to rFVIIa therapy. Despite these complications, the authors concluded that laparoscopic liver biopsy can be performed safely and reliably by using rFVIIa in patients in whom the standard procedure might be contraindicated because of coagulopathy.

The safety and efficacy of rFVIIa in cirrhotic patients with bleeds of the upper gastrointestinal tract was studied in a randomized study of 245 patients with a composite primary endpoint including failure to control bleeds of the upper gastrointestinal tract within 24 h after first dose, failure to prevent rebleeding within 24 h to five deaths, or death within 5 days [29]. There were no significant differences found between the placebo compared to the rFVIIa (eight doses at 100 μg/kg over 30 h) cohosts: failures on composite endpoint were 16 and 14%, respectively ($P = 0.72$).

Patients with normal hepatic function

A recent prospective, randomized, double-blind multicenter study evaluated the efficacy of two different doses of rFVIIa compared to placebo on RBC transfusions for noncirrhotic adult patients undergoing partial hepatectomy [30]. Mean RBC volume transfused was 1024, 1354, and 1036 ml for placebo, 20 μg/kg rFVIIa, and 80 μg/kg rFVIIa, respectively ($P > 0.05$). Similarly, there were no differences in percentage of patients transfused and in intraoperative blood losses. Serious adverse events were not different.

Patients with hemorrhagic stroke

A recent prospective, randomized, double-blind placebo-controlled trial of three doses of rFVIIa compared to placebo was reported in patients presenting with acute (<4 h) hemorrhagic stroke [31]. For the primary outcome of expansion of intracerebral hemorrhage volume 24 h after treatment, the percentage of patients showing expansion was 28, 16, 14 and 11% for the placebo, 40, 80 and 160 μg/kg doses, respectively ($P < 0.05$ treatment cohorts compared with placebo). The percentage mortality was 29, 18, 18 and 19% respectively ($P < 0.05$, treatment cohorts compared with placebo). Impairment scored at 90 days was also improved in the treatment cohorts compared with placebo. Results of a follow-up, completed three-arm clinical trial (placebo, 40 μg/kg, and 80 μg/kg) are pending.

Safety

Of the more than 170 000 standard doses of rFVIIa given after its approval (almost all to patients with hemophilia and inhibitors), only rare (fewer than one in 11 300) thrombotic events have been reported [1]. Thrombotic complications have also been reported with rFVIIa therapy in patients without inhibitors to factor VIII or IX. An acute cerebral vascular accident and death occurred in a clinical trial of rFVIIa (90 μg/kg) before and after minor surgery or dental procedures in patients with factor XII deficiency [32] The last of 10 patients enrolled in an open-label, dose-escalation trial to prevent rebleeding after subarachnoid hemorrhage developed middle cerebral artery thrombosis after receiving rFVIIa [33]. In a high-risk trauma population, three of 40 (7.5%) patients who were deemed at high risk for thrombosis developed thrombotic complications after receiving rFVIIa [34].

Whereas serious adverse events and thrombotic events have been distributed evenly among treatment and

Table 1 Recommendations for administration of recombinant factor VIIa

Currently approved clinical settings
1. Patients with factor VIII or IX inhibitor
   Vigorous bleeding, impending compartment syndrome, or bleeding in critical location: 90 μg/kg every 2–3 h until patient hemostasis is achieved, then less frequently thereafter.
   Persistent bleeding, not life or limb threatening: titrate both dose and interval to obtain adequate hemostasis.
   Prior to invasive procedures: 90 μg/kg initially, subsequent doses, interval, and duration of treatment titrated to bleeding risk.
   No signs of bleeding, stable hemoglobin: rFVIIa not indicated.

Currently nonapproved clinical settings
1. Qualitative, quantitative platelet disorders and life-threatening bleeding unresponsive to platelet transfusion.
   Correct coagulopathy and anemia with platelets, FFP, cryoprecipitate, and red cell transfusions.
   Administer DDAVP and Amicar
   Dialyze if uremic
   rFVIIa 4.8 mg vial[a] (50–100 μg/kg for 100–50 kg patient). If clinical response, titrate dose and interval to maintain adequate hemostasis.
2. Prolonged INR requiring rapid reversal
   (a) Minimal or no active bleeding
10 mg vitamin K intravenously or subcutaneously
   (b) Life or limb at risk
   1.2 mg vial rFVIIa[b], and FFP 15–20 ml/kg, *and* 10 mg vitamin K, i.v. infused over 20 min
3. Uncontrollable hemorrhage associated with trauma, surgery, and liver failure
   (a) Replace consumed/diluted hemostatic factors with FFP, cryoprecipitate, platelet transfusion, red cell transfusions.
   (b) Periodically monitor PT, aPTT, fibrinogen, platelet count, hemoglobin.
   (c) If excessive bleeding continues without apparent response to adequate blood components and no identifiable surgical source has been found, 4.8 mg vial rFVIIa (50–100 μg/kg for 100–50 kg patient). If bleeding does not diminish in 30–60 min, consider one more dose, or surgical exploration.
   (d) Use rFVIIa with caution in patients at increased risk for thrombotic complications:
   after cardiac surgery
   patients with a history of coronary artery disease
   patients with history of venous or arterial thrombosis
   patients with DIC
   patients on ECMO or VAD
   patients with cerebral vascular disease.
4. Congenital factor VII deficiency
   (a) Factor VII activity >25%, expectant management except neurologic, cardiothoracic, or ophthalmologic surgery/trauma.
   (b) Factor VII activity <25% and minor trauma/surgery:
   initial treatment: 10–15 ml/kg FFP
   repeat 3–6 ml/kg at 6–8 h intervals until hemostasis is achieved.
   (c) Factor VII activity <25% and at risk for neuro-, cardiothoracic, ophthalmologic bleeding:
   initial treatment: rFVIIa 1.2 mg vial (20 μg/kg for 70 kg patient) every 2 h until hemostasis is achieved.
   titrate dose and interval to ongoing bleeding risk.
   combined treatment with FFP and rFVIIa at lower doses is a consideration in patients who can tolerate volume infusions.

[a] Currently available in vials of 1.2, 2.4, and 4.8 mg.
[b] 20 μg/kg for a 70 kg patient; subsequent doses of rFVIIa indicated for clinical signs of persistent bleeding, not to maintain a normal PT/international normalized ratio.
aPTT, activated partial thromboplastin time; DDAVP, D-arginine vasopressin; DIC, disseminated intravascular coagulation; ECMO, extracorporeal membrane oxygenation; FFP, fresh-frozen plasma; INR, international normalized ratio; PT, prothrombin time; rFVIIa, recombinant factor VIIa; VAD, ventricular assist device.
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placebo cohorts in several large randomized clinical trials of patients undergoing radical prostatectomy [11], trauma [19], bleeding of the upper gastrointestinal tract [29], or partial hepatectomy [30], there was an uneven distribution of thromboembolic events in the clinical trial of patients with hemorrhagic stroke [31]; total events were two (2%), seven (6%), four (5%), and 10 (10%) for the placebo, 40, 80 and 160 μg/kg cohorts, respectively. Most of these events were arterial, including thrombotic stroke and myocardial infarction. Whether these serious adverse events are attributed to rFVIIa or to a population at risk for these events will need to be determined in a follow-up clinical trial.

A summary of thromboembolic events reported to the US Food and Drug Administration between 25 March 1999 and 31 December 2004 indicated a total of 151 thromboembolic events in settings to unlabeled indications [35•]. These included deep-venous thrombosis (42), cerebral vascular accidents (39), acute myocardial infarctions (34), pulmonary thromboembolus (32), arterial thrombosis (26), and clotted devices (10). Thirty-eight percent of cases had concomitant use of other hemostatic agents. In 36 (72%) of 50 reported deaths, rFVIIa was listed as the probable cause. The authors concluded that randomized clinical trials are necessary to demonstrate safety and efficacy of rFVIIa in non-approved settings. A subsequent report analyzed safety data from 13 clinical trials in patents treated with rFVIIa for cirrhosis, trauma, or reversal of anticoagulant therapy [36•]. The authors reported thrombotic adverse events in 5.3% of patients who received placebo, compared to 6.0% in patients who received rFVIIa ($P = 0.57$).

In cardiac surgery patients, cohort-matched studies [13,14] and a systematic review [37] found no differences in serious adverse events in patients treated with rFVIIa. We reported a patient who had a fatal thrombosis after administration of activated prothrombin-complex concentrate, who had also received two doses of rFVIIa more than 6 h earlier, while supported by extracorporeal membrane oxygenation [38]. Because of this experience, we recommend that patients should not receive combination therapy with both activated prothrombin-complex concentrate and rFVIIa.

On the basis of these reports, use of activated factor concentrates should be used with caution in patients with known hypercoagulability (e.g. history of thrombotic complications, established thrombotic disorders like Factor V Leiden, or antiphospholipid syndrome) or who have excessive bleeding in the setting of disseminated intravascular coagulation or other states of generalized activation of the hemostatic system (e.g. after cardiac surgery, patients on extracorporeal membrane oxygenation or ventricular assist devices) based on the potential for development of localized or systemic intravascular thrombosis.

Dose

A retrospective review of 40 patients with coagulopathic bleeding in a variety of medical and surgical settings from 13 hospitals in an internet-based database (excluding prior history of coagulopathy and trauma patients) who received rFVIIa (15–180 μg/kg, with 38 patients receiving fewer than five doses) found that 32 (80%) achieved complete ($n = 18$) or partial ($n = 14$) cessation of bleeding [20]. Responses occurred in all dose ranges, without any evidence of a dose–response effect; the percentages of complete, partial, or no response were not different at doses of <70 μg/kg, 70–90 μg/kg or >90 μg/kg (Fig. 1). Significantly fewer blood products were administered after rFVIIa therapy. Twenty-three (58%) patients died, reflecting the unstable clinical status of the patients at the decision point for considering rFVIIa therapy. On the basis of this study, we have recommended a non-weight-based dosage strategy in which a 4.8 mg vial administered to an adult patient weighing 50–100 kg represents a 100–50 μg/kg dose (Table 1) [9].

Conclusion

Dose and timing of rFVIIa have yet to be defined in this diverse patient population, and formal prospective trials are needed. Consensus-based recommendations on the use of rFVIIa in nonapproved settings have been developed [39]. In the meantime, the decision on when and where to use rFVIIa for patients with uncontrolled bleeding continues to be one that must be made by individual physicians, assisted by their hospital pharmacotherapeutic or transfusion committees [40].

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 601–602).

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