

Transfusion medicine service policies for recombinant factor VIIa administration

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Recombinant FVIIa (rFVIIa) has been approved for treatment of bleeding in hemophilia patients with inhibitors. It has also been successfully used in nonhemophilia patients with acquired antibodies against FVIII (acquired hemophilia). Pharmacological doses of rFVIIa have been found to enhance the thrombin generation on already activated platelets and, therefore, may also likely be of benefit in providing hemostasis in other situations characterized by profuse bleeding and impaired thrombin generation,¹ such as 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 bleeding situations,⁴⁻⁷ as well as in patients with impaired liver function.^{8,9} To date, case reports, anecdotal experience, and limited clinical trials describe these uses; data from randomized clinical trials are limited. Because of the recent trends in rFVIIa usage in non-approved settings among physicians from various disciplines, significant concerns about its safety, efficacy, and costs have arisen. Additionally, dosing of rFVIIa for these potentially broad clinical applications is not standardized. Currently, 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 pharmacotherapeutics and transfusion committees.¹⁰

Our transfusion medicine service undertook a review of the currently available data and experience regarding rFVIIa therapy and developed educational guidelines and policy recommendations for its potential use in these areas. These were presented and approved by our hospital transfusion committee in July, 2003. Because of concerns regarding use of this drug in the context not only of costs but also for potential adverse events such as unwanted thrombosis, our transfusion committee set forth two conditions for approval of rFVIIa therapy: the initial dose released must be approved by the transfusion medicine service, and, subsequently, a hematology consult is recommended for assistance in managing the patient, along with an assessment of the effect of rFVIIa on clinical outcomes. An educational newsletter summarizing these elements was published in our Laboratory Medicine Newsletter.¹¹ These policies function as our local operating guidelines for rFVIIa and undergo periodic review and revision as relevant new information and data are generated. Our current transfusion service policies for rFVIIa therapy, based on a review of the salient literature, are presented herein.

ABBREVIATIONS: APCC = activated prothrombin complex concentrate; DIC = disseminated intravascular coagulation; ECMO = extracorporeal membrane oxygenator; INR = international normalized ratio; PT = prothrombin time; rFVIIa = recombinant factor VIIa.

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rFVIIa IN HEMOPHILIA PATIENTS WITH INHIBITORS

In hemophilia patients who have developed inhibitors against FVIII (hemophilia A) or F IX (hemophilia B), elective surgery has previously been contraindicated because of the risk of uncontrollable bleeding. However, rFVIIa has been used successfully in major surgery, such as total hip replacement and bilateral knee replacement in a number of hemophilia patients (both hemophilia A and B).^{12,13} A prospective, double-blind, randomized trial in surgery comparing two doses of rFVIIa (35 and 90 µg/kg) administered every 2 hours for the first 48 hours after surgery showed a significant difference in efficacy favoring the high-dose group.¹⁴ Another randomized, double-blind comparative study in joint and muscle bleedings showed that 35 µg per kg as well as 70 µg per kg were safe and reasonably effective.¹⁵ When used in a home-treatment setting starting immediately at the first signs of an upcom-

ing bleed, an average of 2.3 injections of 90 µg per kg was required to obtain a 90-percent prevention of the development of joint and muscle bleeding.¹⁶

The standard (and approved) intravenous (IV) dose of rFVIIa in hemophilia patients with an inhibitor is 90 µg per kg until hemostasis is achieved; for surgical patients, repeated doses are administered every 2 hours until hemostasis is achieved, then less frequently thereafter (Table 1). Doses between 35 and 120 µg per kg have been used successfully in clinical trials, and both the dose and administration interval may be adjusted based on the severity of the bleeding and degree of hemostasis achieved. Most patients are also given antifibrinolytic therapy. Successful use of rFVIIa has also been demonstrated in minor surgery and dental surgery.¹⁷

rFVIIa has been given to hemophilia patients suffering from serious bleedings in the central nervous system, intraperitoneal and retroperitoneal hemorrhage, as well as muscle (compartment syndrome) bleedings. The same

TABLE 1. rFVIIa* dosing policies

Currently approved clinical settings

1. Patients with FVIII or IX inhibitor

- A) Vigorous bleeding, impending compartment syndrome, or bleeding in critical location: 90 µg/kg q 2-3 hr until patient hemostasis is achieved, then less frequently thereafter.
- B) Persistent bleeding, not life or limb threatening: titrate both dose and interval to obtain adequate hemostasis.
- C) Before invasive procedures: 90 µg/kg initially, subsequent doses, interval, and duration of transfusion titrated to bleeding risk.
- D) No signs of bleeding, stable hemoglobin level: rVIIa not indicated.

Currently nonapproved clinical settings

1. Qualitative, quantitative PLT disorders and life-threatening bleeding unresponsive to PLT transfusion.

- A) Correct coagulopathy and anemia with PLTs, FFP, cryoprecipitate, and RBC transfusions.
- B) Administer DDAVP and Amicar.
- C) Dialyze if uremic.
- D) rVIIa 4.8-mg vial (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 IV or SQ.
- B) Life or intracranial hemorrhage risk.
1.2-mg vial rFVIIa,† and FFP 15-20 mL/kg, and 10 mg vitamin K IV infused over 20 min.

3. Uncontrollable hemorrhage associated with trauma, surgery, and liver failure.

- A) Replace consumed/diluted hemostatic factors with FFP, cryoprecipitate, PLT transfusion, RBC transfusions.
- B) Periodically monitor PT, aPTT, fibrinogen, PLT count, hemoglobin level.
- 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 50-100 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:
 - 1) After cardiac surgery.
 - 2) Patients with H/O coronary artery disease.
 - 3) Patients with H/O venous or arterial thrombosis.
 - 4) Patients with DIC.
 - 5) Patients on ECMO or VAD.
 - 6) Patients with cerebral vascular disease.

4. Congenital FVII deficiency.

- A) FVII activity >25%, expectant management except neurologic, cardiothoracic, or ophthalmologic surgery/trauma.
- B) FVII activity <25% and minor trauma/surgery:
Initial treatment: 10-15 mL/kg FFP.
Repeat 3-6 mL/kg at 6- to 8-hr intervals until hemostasis is achieved.
- C) FVII activity <25% and at risk for neuro, cardiothoracic, ophthalmologic bleeding:
 - A. Initial treatment: rVIIa 1.2-mg vial (20 µg/kg for 70-kg patient) q 2 hr until hemostasis is achieved.
 - B. Titrate dose and interval to ongoing bleeding risk.
 - C. Combined treatment with FFP and rFVIIa at lower doses is a consideration, in patients who can tolerate volume infusions.

* Currently available in vials of 1.2 mg, 2.4 mg, and 4.8 mg.

† 20 µg/kg for a 60-kg patient; subsequent doses of rFVIIa indicated for clinical signs of persistent bleeding, not to maintain a normal PT/INR. DDAVP = deamino D-arginine vasopressin; aPTT = activated partial thromboplastin time; H/O = history of; VAD = ventricular assist device.

dose schedule as that recommended in surgery has been used. The overall effective response after 8 and 24 hours was 91 and 90 percent, respectively.¹⁸

rFVIIa IN OTHER CLINICAL SETTINGS

Platelet disorders

The availability of PLT procoagulant phospholipids has been demonstrated to be rate-limiting for the production of thrombin,¹⁹ so that patients with a decreased number of platelets (PLTs) have impaired thrombin generation.²⁰ Single-case reports on a hemostatic effect of rFVIIa in thrombocytopenic (as low as 5000/ μ L) patients have been published.^{2,21} Controlled randomized studies are ongoing to establish the potential role and effective dosage of rFVIIa in patients with thrombocytopenia.²²

Complex surgery and traumas resulting in profuse bleeding

Other settings with potential defective thrombin generation include patients subjected to extensive surgery, as well as patients who have been through severe traumas who have substantial bleeding. Acute trauma in humans has been shown to initiate a number of hemostatic changes that are correlated with the severity of the trauma and hemorrhage.²³ A decrease in the concentration of coagulation factors as well as PLTs occurs due to clotting factor consumption.²³ Hemodilution in severely bleeding patients also contributes substantially to the lowered plasma concentrations of the various proteins and PLTs.²⁴ Most of the plasma substitutes used in hypovolemic patients also contribute to the coagulopathy seen in patients after traumas and excessive bleedings.^{25,26}

A hemostatic effect has been demonstrated after the administration of rFVIIa in a limited number of patients after trauma and bleeding.^{5,6,27} A study of the effect of rFVIIa in a trauma model using swine with an inflicted liver injury reported a significant decrease of the bleeding from the livery injury in the pigs given one single dose of 180 μ g per kg of rFVIIa after the injury as compared with a placebo group. All of these animals were hypothermic and coagulopathic.²⁸ A series of seven trauma patients treated with rFVIIa after failure of conventional measures to achieve hemostasis⁶ reported cessation of diffuse bleeding and correction of abnormal coagulation assays; three of the seven patients died of reasons other than bleeding or of thromboembolism.

A few anecdotal case reports have been published that describe the successful use of rFVIIa in patients with substantial perisurgical bleeding.^{4,7,29} A prospective, randomized study of rFVIIa (20 μ g/kg or 40 μ g/kg) versus placebo perioperatively in 36 patients undergoing radical retropubic prostatectomy found that the cohorts receiving rFVIIa had substantially less median operative blood loss

compared to placebo (1235 mL, 1089 mL, and 2688 mL, respectively).³⁰

Nine patients with coagulopathy and urgent neurosurgical intervention were reviewed after receiving preoperative rFVIIa (40-90 μ g/kg).³¹ Post-rFVIIa coagulation variables normalized as early as 20 minutes after infusion, with no noted procedural or operative complications. No associated thromboembolic complications were observed. Similar results were found in three pediatric neurosurgical patients treated with 90 μ g per kg of rFVIIa.³²

In summary, the experience of rFVIIa use in trauma with excessive bleeding as well as in postoperative profuse bleeding, based largely on case reports, indicates a hemostatic effect of rFVIIa given in doses of 20 to 120 μ g per kg. Our initial dosage approval for administration is recommended to be a 4.8-mg vial, which for an adult patient is a dose range of 50 to 100 μ g per kg for a body weight range of 100 to 50 kg (Table 1). One or two administrations seem to be enough to decrease the bleeding significantly. Controlled randomized studies are, however, required to prove any beneficial effect of rFVIIa in these patients.

CONGENITAL FVII DEFICIENCY

FVII deficiency is a rare coagulation disorder that is characterized by spontaneous bleeding episodes in severely affected patients and bleeding after surgical challenge or trauma in the mildly affected. Plasma-derived FVII concentrates were developed, followed by the development of rFVIIa, both of which have been satisfactorily used in the treatment of FVII deficiency.^{33,34} In a randomized study, 17 FVII-deficient patients were treated with rFVIIa.³⁴ The doses of rFVIIa ranged from 21 to 27 μ g per kg, based on calculations of the dose capable of normalizing the prothrombin time (PT) 15 minutes after injection. The treatment resulted in excellent resolution of all hemarthroses treated. An infant with severe FVII deficiency and massive intracranial hemorrhage was evaluated after administration of rFVIIa at three dose levels: 15 μ g per kg, 22 μ g per kg, and 30 μ g per kg.³⁵ FVII levels were higher than 100 percent between 30 and 180 minutes after each infusion, with mean trough levels above 25 percent at all three dose levels. Our recommended dosage for rFVIIa replacement therapy in congenital FVII deficiency is therefore 20 μ g per kg (Table 1).

ACQUIRED FVII DEFICIENCY

Patients receiving oral anticoagulant therapy

Through vitamin K antagonism, anticoagulant agents induce low levels of functional vitamin K-dependent coagulation factors (factors prothrombin, VII, IX, and X). FVII has been shown to be the earliest and the most sensitive of the coagulation factors to be affected by oral

anticoagulant therapy, monitored indirectly by the international normalized ratio (INR) value. Spontaneous hemorrhages have been reported to occur in approximately 10 to 20 percent of patients receiving oral anticoagulant therapy.^{36,37} Of these, half occur in patients with INR values outside therapeutic range and half in patients with INR values within therapeutic range. These patients also may require urgent reversal of their prolonged INR when invasive procedures are scheduled or after head trauma.

One spontaneous nosebleed in a patient on warfarin with an INR of 2.9 was reported to have been successfully treated with two doses of 80 µg per kg of rFVIIa.³⁸

Another report describes the use of rFVIIa in seven adult patients with prolonged INR, three of whom required surgery. The doses administered ranged from 20 to 90 µg per kg, and all patients were reported to have a positive outcome.³⁹ These observations indicate that rFVIIa may be used to reverse the effect of warfarin or other vitamin K-antagonist therapies 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 FVIIa for reversal of excessive anticoagulation with Coumadin support a dosage of 20 µg per kg, or 1.2 mg for an adult patient.^{40,41} It is important to note that vitamin K and plasma therapy (15-20 mL/kg, or at least 4 units) should also be administered concomitantly to correct deficiencies of functional prothrombin, IX, and X (Table 1). Controlled randomized studies are required to establish the optimal dose of rFVIIa.

Patients with impaired liver function

The liver is the principal site for synthesis and clearance of coagulation factors, components of the fibrinolytic system, and naturally occurring anticoagulants. Cirrhotic patients do not generally experience bleeding episodes apart from upper GI bleeding, but they are at an increased risk of bleeding from routine procedures such as liver biopsy and also during major surgery such as liver transplantation.⁴²

A hemostatic effect of rFVIIa has been proven in a limited number of liver disease patients.^{8,9} In one clinical trial, 10 cirrhotic patients whose PT did not correct to within 2 seconds above the control reference value were given three successive dosages of rFVIIa (5, 20, or 80 µg per kg) during a 3-week period in a randomized study.⁴³ The PT transiently corrected to normal in all three dosage groups.

In a single-center study, six patients received 80 µg per kg rFVIIa before liver transplantation.⁴⁴ The authors concluded that the single dose significantly reduced transfusion requirements when compared with the matched controls and that further randomized controlled studies were needed in patients undergoing liver trans-

plantation to establish the optimal and safe dose of rFVIIa. A multicenter trial studied 71 patients with advanced liver disease who were undergoing laparoscopic liver biopsy.⁴⁵ 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 minutes. One thrombotic event and one case of disseminated intravascular coagulation (DIC) were reported, not felt by the authors to be related to rFVIIa therapy. Despite these complications, the authors concluded that these results suggest 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.

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 (<1:11,300) thrombotic events have been reported.¹ Five patients with thromboembolic events have been reported (two patients with hemophilia, one with acquired hemophilia, one with Glanzmann thrombasthenia, and one with von Willebrand disease). Six patients developed acute myocardial infarction in association with rFVIIa treatment (three hemophilia patients, two with acquired hemophilia, and one with uremic thrombocytopenia). Five out of the six patients were over 70 years old, and two of the hemophilia patients had a history of cardiovascular disease, which also was the case in the two patients with acquired hemophilia. Cerebrovascular disorders were reported in four patients, three of whom were more than 55 years old, one with hemophilia and the others having acquired hemophilia.

Thrombotic complications have also been reported with rFVIIa therapy in patients without inhibitors to FVIII or IX. A review of patients with FXI deficiency reported a serious adverse event in a clinical trial of rFVIIa (90 µg/kg) before and after minor surgery or dental procedures.⁴⁶ This occurred in an elderly male patient with a history of acute myocardial infarction, who experienced an acute cerebral vascular accident and who subsequently died during treatment. The last of 10 patients enrolled in the open-label trial, dose-escalation trial to prevent rebleeding after subarachnoid hemorrhage developed middle cerebral artery thrombosis after receiving rFVIIa.⁴⁷ In a high-risk trauma population, 3 of 40 (7.5%) patients who were deemed at high risk for thrombosis developed thrombotic complications after receiving rFVIIa.⁴⁸

We reported a patient who had a fatal thrombosis after administration of activated prothrombin complex concentrate (APCC) who had also received two doses of rFVIIa, more than 6 hours earlier, while supported by extracorporeal membrane oxygenation.⁴⁹ Because of this experience, we recommend that patients should not receive combination therapy with both APCC and rFVIIa, and that clini-

cians confirm the adequacy of anticoagulation for patients on extracorporeal membrane oxygenator (ECMO) or ventricular assist device (VAD). Because the thrombotic potential of rFVIIa is currently felt to be less than that for APCC, our use of rFVIIa in this setting is indicated for patients that satisfy the following three criteria: life-threatening bleeding, no identifiable surgical source, and failure to respond to blood component therapy.

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 FV Leiden, antiphospholipid syndrome, etc.) or who have excessive bleeding in the setting of DIC or other states of generalized activation of the hemostatic system (e.g., after cardiac surgery, patients on ECMO or VAD) based on the potential for development of localized or systemic intravascular thrombosis.

DISCUSSION

A review of our transfusion service for 2002 and 2004 indicated that 86 patients received rFVIIa therapy for nonapproved indications (Table 2). The mean dose administered for all of these patients was 8.3 ± 7.7 mg (range, 1.2-60 mg) at a mean cost of \$6805 per patient. Over this same interval, eight patients with hemophilia and inhibitors received a mean dose of 75.7 ± 80.8 mg at a mean cost of \$62,113 per patient. Because of concerns regarding off-label use of this drug in the context not only of costs but also for potential adverse events such as unwanted thrombosis, the Barnes-Jewish Hospital Transfusion Committee has set forth two conditions for requests for rFVIIa: the initial dose released must be approved by the transfusion medicine service, and, subsequently, a hematology consult is recommended for assistance in managing supporting care

and evaluation of the appropriateness of subsequent doses as well as the effect of rFVIIa on clinical outcomes. A recent review of 19 patients with acute warfarin-associated intracranial hemorrhage over this same period at our institution, who received rFVIIa as well as vitamin K and fresh frozen plasma (FFP) for treatment, found that treatment was associated with rapid correction of INR and that single doses appeared safe in this high-risk population.⁵⁰

A retrospective review of 40 patients with coagulopathic bleeding in a variety of medical and surgical settings from 13 hospitals in a web-based database (excluding prior history of coagulopathy and trauma patients) who received rFVIIa (15-180 μ g/kg, with 38 patients receiving fewer than five doses) found that 32 (80%) achieved complete (n = 18) or partial (n = 14) cessation of bleeding.⁵¹ 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 less than 70 μ g per kg, 70 to 90 μ g per kg, or greater than 90 μ g per kg. 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. An accompanying editorial concluded that dose and timing of rFVIIa have yet to be defined in this diverse patient population, and formal prospective trials are needed; and that 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.¹⁰

CONCLUSION

Hospital-based transfusion service guidelines policies for rFVIIa therapy need to be implemented to aid individual

TABLE 2. rFVIIa utilization

Series	2002		2003		2004	Total
	January-June	July-December	January-June	July-December	Jan-June	
All patients (number)	5	14	26	47	38	130
Doses (number)	18	45	121	121	78	383
Mean \pm SD* total dose (mg)	12.2 ± 9.1	12.0 ± 12.1	21.2 ± 50.5	10.4 ± 13.0	8.6 ± 13.5	12.5 ± 26.0
Range	2.4-24	2.4-48	2.4-246	1.2-60	1.2-84	1.2-246
On-label FVIII inhibitors (number)	2	0	2	2	2	8
Doses (number)	9	0	79	12	26	126
Mean \pm SD total dose (mg)	14.4 ± 6.8	NA	125 ± 121	57 ± 2.5	43.2 ± 57.7	75.7 ± 80.8
Range	9.6-19.2	NA	4-246	55.2-58.8	2.4-84.0	2.4-246
Off-label (number)	3	14	24	45	36	122
Doses (number)	9	45	42	100	52	248
Mean \pm SD total dose (mg)	10.8 ± 11.6	12 ± 12.1	8.2 ± 4.8	8.3 ± 8.6	6.7 ± 5.2	8.3 ± 7.7
Range	2.4-24	2.4-48	2.4-24.5	1.2-60	1.2-27.6	1.2-60

* SD = standard deviation.

physicians and to provide a framework for oversight of its efficacy, safety, and costs in nonapproved settings.

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