Recombinant Factor VIIa in the Treatment of Bleeding

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Key Words: Recombinant factor VIIa; Liver failure; Drug-induced coagulopathies; Platelet disorders; von Willebrand disease; Factor VII deficiency; Postsurgical bleeding; Posttrauma bleeding

DOI: 10.1309/D0G0C96V05CJ5B4J

Abstract

Recombinant factor VIIa (rFVIIa) has become available for treating people with hemophilia with inhibitors who experience bleeding or require surgery. It has become apparent that rFVIIa is useful in controlling bleeding in a variety of clinical situations. This review attempts to collate and summarize the nonhemophilia applications of rFVIIa. The theoretical mechanism for the coagulation and hemostatic effects of rFVIIa are discussed. The dosage and clinical administration are described.

The potential uses for patients with liver disease, anticoagulation-induced bleeding, surgery, thrombocytopenia, thrombasthenia, von Willebrand disease, and other bleeding disorders are reviewed. The use of rFVIIa is evolving, and the indications, dosage, and precautions or contraindications need to be further described and defined. It is an expensive therapy and needs to be prescribed judiciously. This review is meant to be an introduction to this new hemostatic reagent. The uses for rFVIIa will evolve as more studies are published.

New advances in medicine are evaluated by their efficacy in clinical trials. However, in certain areas, the numbers of specific patients or the heterogeneity of the patients make prospective clinical trials difficult. In the area of bleeding, the clinical situations often are so varied and multifactorial that physicians have accepted the investigational use of agents to treat life-threatening hemorrhage. This has become the case for treatment of hemorrhage with recombinant factor VIIa (rFVIIa).

Originally, rFVIIa was developed for the treatment of bleeding complications in patients with hemophilia with alloantibodies (inhibitors) against exogenous factor VIII or IX.1-11 In 1988, rFVIIa was used successfully in patients with inhibitors to these factors.12 Recently, the effectiveness and safety of rFVIIa in patients with hemophilia with inhibitors has been reported in the hemophilia research society registry.13 rFVIIa has become available as a recombinant preparation and also has been used in nonhemophilic conditions. At present, the only US Food and Drug Administration–approved use of rFVIIa is for the treatment of patients with hemophilia with inhibitors. We describe the uses of rFVIIa in conditions unrelated to hemophilia and the treatment of acquired inhibitors of factors VIII and IX. Some of the limitations in the use of rFVIIa at present are related to the cost of the drug. As clinical use and experience increase and the cost of rFVIIa decreases, the indications for the use of rFVIIa may change drastically. rFVIIa might become the treatment of choice in selected cases of massive hemorrhage, but more data are needed before this occurs.

Hemostasis is a physiologic mechanism that maintains blood in a fluid state within the circulation. The coagulation of blood is maintained by cellular components and soluble plasma proteins. In response to vascular injury, circulating
platelets adhere, aggregate, and provide cell surface phospholipids for the assembly of blood clotting enzyme complexes, thrombin activation, and fibrin formation. Simultaneously fibrinolysis is initiated.

At the site of injury, tissue factor (TF) and factor VIIa activate factors X and IX. Thrombin is generated, and fibrin is formed. [14][15] When there are low levels of factor VIII or IX, the formation of thrombin is slow [Figure 1]. When pharmacologic doses of rFVIIa are given, there is a marked enhancement of thrombin formation. This increase in the thrombin burst occurs after direct rFVIIa activation of factors IX and X on the surface of activated platelets (even in the absence of factor VIII or IX). It is postulated that the thrombin-generating capacity of rFVIIa is enhanced substantially by platelets accumulating at the site of vascular damage [Figure 2]. This increase in the rate of thrombin formation with large doses of rFVIIa permits the formation of fibrin, which is less susceptible to lysis. The decrease in fibrinolysis might be due to an increase in thrombin-activatable fibrinolysis inhibitor and an increase in factor XIIIa. The rFVIIa seems to work in a TF-independent manner directly on factors IX and X on the phospholipid surface of activated platelets. rFVIIa is able to activate factor X on phospholipid vesicles, activated platelets, or monocytes independent of TF, although the TF-independent generation of thrombin is much less efficient than the TF-dependent thrombin generation by rFVIIa. [16] Impaired thrombin formation caused by a low number of platelets with functional defects due to consumptive or dilutional processes might be overcome by treatment with rFVIIa (Figure 1).

It is important to note that although global tests such as the prothrombin time (PT) are shortened by in vivo treatment with rFVIIa, there is little evidence to suggest that substantial fibrin is formed or remains anywhere except where there is tissue trauma.

rFVIIa has become available as a recombinant preparation and has been used in hemophilia and in nonhemophilia conditions. A large number of case reports and studies show that rFVIIa might be effective for prevention and treatment of bleeding in patients with inherited and acquired hemophilia, overanticoagulation, renal failure, liver disease, liver transplantation, intractable bleeding, platelet disorders, and congenital severe factor VII deficiency. [17] However, most are anecdotal case reports and small series. This review attempts

Figure 1 [Figure 1] Tissue factor–dependent action of recombinant factor VIIa. The tissue factor–dependent pathway is shown by gray shading. Dashed lines represent site of major inhibitors. AP, α-antiplasmin; APC, activated protein C; FDP, fibrin split products; PAI, plasminogen activator inhibitor; PC, protein C; PS, protein S; TAFI, thrombin-activatable fibrinolysis inhibitor; TFPI, tissue factor pathway inhibitor; TM, thrombomodulin; TPA, tissue plasminogen activator; UK, urokinase.
to collate these reports and discuss the reported uses of rFVIIa [Table 1].

**Liver Disease**

Liver disease might result in substantial reduction in the synthesis of factors involved in coagulation and in factors controlling fibrinolysis.18 Also, there might be moderate thrombocytopenia. When there is bleeding, it often is in the upper gastrointestinal tract. There often is a decrease in the synthesis of the vitamin K–dependent coagulation factors, and fresh frozen plasma (FFP) and vitamin K are used to control bleeding in these cases. The use of large amounts of FFP might be limited by the patient’s ability to cope with the required fluid load. Prothrombin complex concentrates (PCCs) have been used to treat acquired factor VIII or IX inhibitors, but they are associated with adverse effects such as allergic reactions, heparin-induced thrombocytopenia, and thromboembolic complications, including disseminated intravascular coagulation (DIC).19 Activated PCCs such as FEIBA, Proplex T, and Autoplex T (Baxter Healthcare, Deerfield, IL) have a higher margin of safety with much less risk of viral transmission and a low level of thrombotic events.20-23

rFVIIa has been used to treat patients with acute hepatic trauma, bleeding after liver biopsy, chronic liver disease with cirrhosis, and after liver transplantation.24 rFVIIa seems to be safe and effective for patients in these situations and permits several invasive procedures without the complications of bleeding. This has been studied in experimental studies and in patients with liver failure. A study of the effects of rFVIIa on bleeding after a grade V liver injury on coagulopathic pigs revealed that the blood loss was reduced when rFVIIa was used as an adjunct to abdominal packing.25 Testing in anesthetized swine revealed that administration of rFVIIa early after injury decreased bleeding and prolonged the time from injury to death after experimental trauma.26,27 There was no evidence of thrombosis in the vital organs. A study done to evaluate the efficacy of rFVIIa in cirrhosis showed improvement in clot formation with rFVIIa, but there was no evidence of antifibrinolytic effect in patients with cirrhosis or in patients undergoing orthotopic liver transplantation as evidenced by clot lysis time.28

Correction of the PT in nonbleeding patients with cirrhosis was shown in a study with escalating doses of rFVIIa.29 There was a transient improvement in PT with the 3 doses tested, and no adverse effects were noted. The effect of rFVIIa on the PT in 10 patients with cirrhosis with ongoing variceal bleeding was studied in a single-center, open-label trial.30 rFVIIa normalized the PT in all patients within 30 minutes with immediate bleeding control, and the effect lasted 2 to 4 hours. There were no signs of DIC and no deaths. Chuansumrit et al31 studied the effect of rFVIIa in normalizing the PT in 5 children with liver diseases, 3 of whom had massive bleeding. The study showed that rFVIIa was effective in normalizing the coagulation parameters, stopping bleeding episodes, and permitting invasive procedures.

There are a number of other case studies reported on the use of rFVIIa in liver diseases. For example, Berthier et al32 reported the use of rFVIIa in 2 patients with cirrhosis to treat persistent bleeding following dental extractions; the bleeding was not controlled despite repeated administration of FFP in one of them. Bleeding stopped promptly in both patients but recurred in one who did not receive concomitant local treatment. Similarly, Jeffers et al33 evaluated the effect of 4 doses of rFVIIa (5, 20, 80, and 120 µg/kg) on the correction of PT and the time to achieve hemostasis in patients with cirrhosis with coagulopathy who were undergoing laparoscopic liver
biopsy. The study included 71 patients with advanced liver disease with a platelet count of $6 \times 10^{11} / \mu L$ ($6 \times 10^9 / L$) or less and a PT 3 to 15 seconds higher than the reference range. Normalization of PT and time to hemostasis were measured. The duration of normalization of PT was longer in patients treated with higher doses of rFVIIa. Hemostasis was achieved in 74% of the patients in 10 minutes. None required transfusions or operative intervention to control bleeding. Complications reported were 1 thrombotic event (portal vein thrombosis) and 1 event of DIC, which were considered not related to treatment. Kositchaiwat and Chuansumrit\(^{34}\) report their experience with use of rFVIIa in 7 patients with prolonged PTs due to liver disease. The patients’ PTs were 3 seconds longer than those of control subjects and did not respond to the administration of FFP and vitamin K. With the use of rFVIIa, percutaneous liver biopsies and endoscopy were performed with no reported adverse reactions.

Data on the use of rFVIIa before procedures to treat coagulopathy-associated hepatic dysfunction or the effects of warfarin were studied, and the use of rFVIIa was reported to reverse the coagulopathy with no significant complications. The PT international normalized ratio (INR) reduced from a mean of 2.8 to 1.4 after rFVIIa in a study of 37 patients, and the PT international normalized ratio (INR) reduced from a mean of 2.8 to 1.4 after rFVIIa in a study of 37 patients, and in another study of 17 patients, the average pretreatment PT was 28.6 seconds and the average posttreatment PT was 15.1 seconds following a single dose of rFVIIa.\(^{35,36}\)

rFVIIa has been used during and after liver transplantation with effective hemostasis achieved. There have been reports of successful preoperative and postoperative administration of rFVIIa to prevent bleeding during liver transplantation.\(^{37,38}\) Shami et al\(^{39}\) reviewed their experience with rFVIIa before liver transplantation in patients with fulminant liver failure. rFVIIa was more effective than FFP in transiently correcting laboratory parameters of coagulopathy, was associated with less frequent anasarca, permitted the performance of invasive procedures, and was associated with slightly better overall survival. Another pilot study on transfusion requirements in liver transplantation was used to assess the effects of rFVIIa on coagulation variables, and thromboelastography was used to monitor hemostasis during liver transplantation. Compared with the control group, there was significant shortening of the PT and activated partial thromboplastin time (aPTT). The mean PT improved from 21.8 to 11.7 seconds, and the mean aPTT improved from 38.5 to 33.7 seconds in the study group following administration of rFVIIa.\(^{40}\)

### Drug-Induced Coagulopathy

Patients receiving oral anticoagulant treatment have abnormally low levels of functional vitamin K–dependent coagulation proteins and, consequently, an increased risk of hemorrhagic complications.\(^{41,42}\) Drug-induced hemorrhagic events have been associated with warfarin. The incidence of hemorrhage has been reported around 0.6% to 0.7% per month at a therapeutic INR. Plasma or PCCs have been used to treat bleeding associated with oral anticoagulants, but these products have been associated with an increased risk of infections and thromboembolic complications, respectively. rFVIIa has been tested in rats and humans treated with anti–vitamin K drugs, and it completely normalized the PT in animals and humans with acquired deficiencies of the vitamin K–dependent factors.\(^{43}\)

Girard et al\(^{44}\) evaluated the effect of different doses of intravenous rFVIIa in healthy volunteers who had an INR greater than 2 while taking acenocoumarol. They also studied a population pharmacokinetics model for rFVIIa clotting activity after injection of rFVIIa in 28 healthy volunteers who were undergoing anticoagulation therapy with acenocoumarol. The volume of distribution at steady state seemed to be significantly dose-dependent; the estimated clearance was 2.4 L/h. The dose of rFVIIa that produced a 50% drop of INR was estimated to be 2.2 µg/kg.\(^{44}\)

Muleo et al\(^{45}\) reported completely satisfactory results with the use of rFVIIa in 4 patients, 3 with liver disease and 1 receiving oral anticoagulant therapy before surgery. In a similar type of study, Deveras and Kessler\(^{46}\) used rFVIIa to treat 13 patients with critically high INRs who required immediate reversal of warfarin-induced anticoagulation. Indications for the use of rFVIIa included an INR of more than 10 in 5 high-risk patients, 4 with clinical hemorrhage, and 4 undergoing diagnostic or therapeutic procedures. The PT and INR were measured before and after administration of rFVIIa. The investigators concluded that rFVIIa was safe and effective for correcting critically prolonged INRs and that it can reverse warfarin-induced bleeding.

An open, multicenter pilot trial is underway to determine the effect of rFVIIa administered to patients experiencing a bleeding episode due to vitamin K antagonists.\(^{41}\) Veshchev et al\(^{47}\) describe a 52-year-old man, a mechanical valve recipient with warfarin-induced coagulopathy, who had an acute coronary occlusion complicated by cardiac arrest. A nose-bleed and oropharyngeal, pulmonary, and gastrointestinal bleeding subsequently developed. He was treated with transfusion of packed RBCs, platelets, and FFP and was given 2 boluses of rFVIIa, after which the bleeding stopped. No adverse effects of rFVIIa were observed, and there was no reocclusion of the implanted stent.\(^{49}\)
The newer anticoagulant fondaparinux is being used postoperatively to prevent venous thrombosis. Bijsterveld et al\(^{50}\) studied the effect of rFVIIa in neutralizing the anticoagulant effects of subcutaneous fondaparinux. In a randomized, placebo-controlled study of 16 healthy volunteers, rFVIIa normalized the prolonged PT, aPTT, and thrombin time induced by fondaparinux. The baseline PT, which was 13.2 seconds, was prolonged to 14.3 seconds with fondaparinux and corrected to 9.2 seconds following administration of rFVIIa. The baseline PTT, which was 33.5 seconds, was prolonged to 38.8 seconds with fondaparinux and corrected to baseline following rFVIIa administration. The duration of this effect ranged from 2 to 6 hours after rFVIIa injection. The authors concluded that rFVIIa effectively normalizes coagulation times and is useful for reversing the anticoagulant effect of fondaparinux in cases of serious bleeding complications.\(^{50}\)

### Platelet Disorders

There is evidence supporting the role of the factor VII tissue-dependent coagulation system in the initial platelet activation for coagulation.\(^{51}\) Infusion of rFVIIa has been shown to shorten the bleeding time in rabbits. Kristensen et al\(^{52}\) reported a reduction in bleeding time in 55 (52.4\%) of 105 patients with thrombocytopenia who received an infusion of rFVIIa. No major adverse effects related to the drug study were observed with the exception of an anaphylactoid reaction in 1 patient. Nine infusions of rFVIIa were given to 8 patients with thrombocytopenia with overt bleeding. Bleeding decreased in all patients and stopped in 6.\(^{52}\)

The mechanism of action of rFVIIa, ie, increased thrombin generation on the membrane of activated platelets, might suggest potential use of rFVIIa in thrombocytopenia and thrombocytopathy.\(^{53}\) Kjalke et al\(^{54}\) studied the effect of rFVIIa in promoting thrombin generation using 2 in vitro models, a reconstituted model and a plasma-based model. In both systems, a platelet density–dependent lowering of the thrombin generation peak was observed. The magnitude of rFVIIa was most pronounced in the plasma-based model. These data suggested that rFVIIa might help adhesive hemostasis at low platelet densities by increasing the initial thrombin generation, thereby compensating for the low platelet number.\(^{54}\)

rFVIIa seems effective and relatively safe for the treatment of bleeding and for surgical prophylaxis in patients with Glanzmann thrombasthenia.\(^{34,55-59}\) In a report about 7 patients with congenital bleeding disorders (Glanzmann thrombasthenia, 5; Bernard-Soulier syndrome, 1; platelet-type pseudo–von Willebrand disease [vWD], 1; acquired thrombocytopathy associated with myelodysplasia and uremia, 2), rFVIIa was well tolerated.\(^{60}\) There was 1 published case of thromboembolism as a postoperative complication in one of the patients.\(^{60}\) A 68-year-old man with Glanzmann thrombasthenia and recurrent nonulcer duodenal bleeding had to undergo duodenectomy because of persistent bleeding. rFVIIa was given, and surgery was done successfully while he was receiving rFVIIa. Neither major blood loss nor other complications occurred postoperatively.\(^{61}\) There has been a case report of the use of rFVIIa to treat postoperative hemorrhage following lumbar discectomy in a 33-year-old woman with Glanzmann thrombasthenia and anti-HLA alloantibodies.\(^{59}\) Successful control of recurrent nosebleeds in 2 teenage boys with Bernard-Soulier syndrome has been reported.\(^{62}\)

Tengborn and Petruson\(^{63}\) describe a 2-year-old boy with Glanzmann thrombasthenia who was treated successfully with rFVIIa for severe refractory epistaxis. Poon et al\(^{58,64}\) who administered rFVIIa to 4 pediatric patients with Glanzmann thrombasthenia for 24 uncontrollable bleeding episodes and 1 surgical prophylaxis, reported bleeding control in all but 1 bleeding episode. van Buuren and Wielenga\(^{61}\) reported the use of rFVIIa in a patient with Glanzmann thrombasthenia and mild thrombocytopenia during a Billroth II gastrectomy for recurrent duodenal bleeding.

d’Oiron et al\(^{65}\) used rFVIIa as first-line therapy in 3 patients with Glanzmann thrombasthenia and anti–platelet glycoprotein IIb/IIIa isoantibodies who were scheduled for invasive procedures. The clinical efficacy and tolerance was excellent in 2 patients, but the third patient had prolonged traumatic nasal bleeding and a thromboembolic complication 5 days after the rFVIIa therapy was discontinued.\(^{65}\) International registry data on the use of rFVIIa in congenital platelet disorders show that it is relatively safe and effective when used in Glanzmann thrombasthenia. The registry received reports about 28 patients with Glanzmann thrombasthenia, and there were 2 adverse effects reported, which were thrombotic events.\(^{58,65,66}\) One of the shortcomings of the registry data is the heterogeneity of the treatment protocol, including dosage, number of doses used, duration of treatment, and mode of treatment. The data are not yet sufficient to define the optimal regimens for various indications such as the type of bleeding or the type of procedure.\(^{58}\)

Gerotziafas et al\(^{67}\) describe 2 patients with severe thrombocytopathy and life-threatening bleeding who were treated successfully with rFVIIa. One was a 75-year-old man with Waldenström macroglobulinemia treated with fludarabine and who had severe nasal bleeding secondary to autoimmune thrombocytopenia that was not controlled by conventional means. The second patient was a 52-year-old woman with precursor B-cell lymphoblastic leukemia and severe thrombocytopenia secondary to chemotherapy, complicated by massive gastrointestinal bleeding. Bleeding was controlled
promptly in both patients, and no adverse effects due to rFVIIa were observed.\textsuperscript{67} Severe bleeding due to acquired thrombocytopenia related to myelodysplastic syndrome was reported to have been controlled effectively with rFVIIa.\textsuperscript{68}

Meijer et al\textsuperscript{68} describe a 76-year-old man with colon carcinoma and myelodysplastic syndrome who had surgery for liver metastasis and developed profuse postoperative gastrointestinal bleeding on the eighth day that did not respond to platelet concentrates, desmopressin, and tranexamic acid. Bleeding promptly stopped with administration of rFVIIa.\textsuperscript{68}

rFVIIa was reported to have been used in a Jehovah’s Witness with autoimmune thrombocytopenia who needed a splenectomy. Postsplenectomy hemorrhage developed, which was controlled successfully with rFVIIa.\textsuperscript{59} Because rFVIIa is not derived from blood, the product is acceptable to Jehovah’s Witnesses.\textsuperscript{59,70}

High-dose rFVIIa is postulated to act on platelets and enhance thrombin generation, which might help provide hemostasis in patients with thrombocytopathies by several mechanisms.\textsuperscript{71} Enhanced thrombin generation provides a strong signal for recruitment of other platelets and might provide mechanisms for bypassing the specific defect in thrombocytopathy. Thus, high-dose rFVIIa has been used to correct bleeding in patients with various thrombocytopathies, including Glanzmann thrombasthenia, Bernard-Soulier syndrome, and uremia.

**Renal Failure**

Acute renal failure is associated with uremic platelet dysfunction and leads to impaired primary hemostasis. Bleeding associated with uremia is treated with dialysis, transfusion of cryoprecipitate, desmopressin, and correction of the underlying cause. rFVIIa has been effective short-term symptomatic treatment for controlling the bleeding associated with uremic platelet dysfunction, thrombocytopenia, or both.\textsuperscript{72} There has been a report of prompt control of bleeding in a 12-year-old patient with end-stage renal insufficiency.\textsuperscript{73}

**Nonhemophilic Bleeding Disorders**

rFVIIa has been used investigationally in patients with hereditary bleeding disorders other than hemophilia, eg, factor VII deficiency, antibody to other clotting factors, and platelet disorders such as Glanzmann thrombasthenia.

Factor VII deficiency is a rare autosomal bleeding disorder that can cause severe bleeding when levels are below 1\%. Treatment consists of FFP, PCCs, or factor VII concentrates. rFVIIa is a useful alternative and seems to be a safe and effective treatment modality. Mariani et al\textsuperscript{74} described 17 patients treated for 27 spontaneous bleeding episodes and 7 major and 13 minor surgical interventions. Hemostasis was secured in the 7 major and 13 minor surgical interventions. There were no side effects and no evidence of thrombotic tendency. All bleeding episodes were controlled effectively.\textsuperscript{74}

Continuous infusion might be better because repeated doses have to be given because of the short half-life of factor VII.\textsuperscript{58,75} Jimenez-Yuste et al\textsuperscript{76} describe a 30-year-old woman with moderate factor VII deficiency and HIV infection who underwent cesarean delivery. She had a history of frequent bleeding episodes during childhood, including recurrent epistaxis, bleeding following dental extraction, and melena treated with FFP. She was treated with a bolus dose of rFVIIa before the cesarean section followed by continuous infusion of rFVIIa and did not have any bleeding complications. Wong et al\textsuperscript{77} describe an infant with severe factor VII deficiency (factor VII protein, 0% [0.00]) and massive intracranial hemorrhage who was treated successfully with rFVIIa. rFVIIa was well tolerated, hemostasis was effective, and there was a good clinical outcome and no evidence of hypercoagulation.\textsuperscript{77} There has been a case report on use of rFVIIa for short-term oral surgery prophylaxis in patients with severe congenital factor VII deficiency.\textsuperscript{78} rFVIIa, when used with endometrial ablation, reportedly controlled bleeding in a patient with intractable menorrhagia secondary to factor VII deficiency.\textsuperscript{79}

A dose kinetic study with rFVIIa was performed in 5 patients with severe congenital deficiency of factor VII to evaluate the true kinetic parameters of rFVIIa without the interference of factor VII.\textsuperscript{80} No differences were observed between the dosages with respect to total body clearance, volume of distribution area, or mean residence time. These findings suggest that the pharmacokinetics of rFVIIa are dose-dependent.

There was another case report on the use of rFVIIa in factor XI deficiency, which could be hereditary or acquired. The patient was a 75-year-old woman with chronic myelomonocytic leukemia and an acquired factor XI deficiency (factor XI level, 5% [0.05]) related to factor XI inhibitor (38 Bethesda units) who needed therapeutic drainage of a pleural effusion. Small doses of rFVIIa were used to achieve hemostasis, and the procedure was done successfully with no adverse effects.\textsuperscript{81}

Two siblings affected by type III vWD with precipitating alloantibodies against von Willebrand factor (vWF) were treated effectively with rFVIIa for oral surgery.\textsuperscript{82} Grossmann et al\textsuperscript{83} reported continuous infusion of rFVIIa in the treatment of a patient with type III vWD and alloantibodies against vWF. A 51-year-old man with type III vWD (factor VIII level, 1% [0.01]; vWF level, <1%; vWF/ristocetin cofactor,
<1%) sought care because of recurrent nosebleeds. He was treated with an rFVIIa-based treatment protocol with an initially good response, but subsequently he had a poor response that was managed effectively with a factor VIII–vWF scheme. He was readmitted with another bleeding episode that did not respond to continuous infusion of rFVIIa combined with tranexamic acid.

Another patient with vWD and recurrent gastrointestinal bleeding due to angiodysplasia had inadequate responses to vWF replacement and medical and endoscopic treatment, including resection of the affected bowel and frequent blood transfusions. Therapy with rFVIIa was started at home, and bleeding was controlled rapidly without the need for blood transfusions. An elderly man with life-threatening hematuria and gastrointestinal bleeding due to acquired vWD associated with monoclonal gammopathy of undetermined significance was treated successfully with rFVIIa. There are other case reports supporting the use of rFVIIa in patients with acquired vWD for bleeding or prophylactically during surgery.

Bleeding associated with amyloid-associated factor X deficiency might be difficult to control with plasma or PCC. Splenectomy ameliorates factor X deficiency. Administration of rFVIIa achieved hemostasis and made splenectomy feasible in a 63-year-old woman with amyloid-associated factor X deficiency.

**Transplantation**

Off-label use of rFVIIa has been reported following bone marrow transplantation. Blatt et al reported the use of rFVIIa in 3 patients (ages 8.8 to 19 years) with pulmonary hemorrhage (1 patient), hemorrhagic cystitis (3 patients), and gastrointestinal bleeding (2 patients). Transient clinical responses in gross hematuria in 2 patients and in pulmonary hemorrhage were noted within several days of starting rFVIIa, but bleeding in a new site in 2 patients and renewed bleeding of the initial site in the third patient resulted in discontinuation of the drug. No toxic or adverse effects were observed after rFVIIa administration. A case report describes the use of rFVIIa in a man with acute myeloid leukemia following bone marrow transplantation. He had severe persistent bleeding with a low platelet count, abnormal PT and PTT, and did not respond to the conventional treatment. Immediate resolution of bleeding was observed after 2 doses of rFVIIa.

rFVIIa was studied in 6 patients undergoing orthotopic liver transplantation for Child B or C cirrhosis. rFVIIa was given at a dose of 80 µg/kg at the start of the operation. Blood loss and perioperative transfusion requirements were compared with those for matched control subjects. The study group had significantly lower blood loss and transfusion requirements. The effect of rFVIIa on blood loss was evaluated in patients with cirrhosis undergoing orthotopic liver transplantation. Thrombin generation was enhanced in a localized and time-limited manner, but there was no difference in fibrinolysis and no evidence of intravascular coagulation.

**Pregnancy**

The use of rFVIIa was reported in a pregnant woman with factor VIIa levels of 1%. rFVIIa had been used prophylactically during pregnancy, and she did not manifest symptoms or signs of excessive bleeding during labor or the puerperium. A woman with a moderate factor VII deficiency and a history of bleeding received rFVIIa continuously during a cesarean section and had no bleeding complications. A pregnant woman with DIC and severe post–cesarean section intra-abdominal bleeding not responding to standard treatment was treated successfully with rFVIIa. Severe intra-abdominal bleeding after cesarean section in a pregnant patient with DIC was reported to have been controlled successfully with rFVIIa.

**Surgery**

rFVIIa has been used in numerous types of surgery to control bleeding due to preexisting conditions or to manage severe surgical bleeding. Cardiac surgery has been one of the more common situations for the treatment of surgical bleeding. rFVIIa has been used in infants and in elderly people. In 1 report in which 5 patients were treated with a single dose of 30 µg/kg, the blood loss dropped from a mean of 4,170 mL (range, 650-8,000 mL) to 262.5 mL (range, 220-334 mL). The plasma factor VII level increased an average of 18-fold, and the PT was reduced markedly.

Substantial postoperative hemorrhage occurs in 3% to 5% of patients after cardiac surgery with cardiopulmonary bypass; rFVIIa might benefit these patients. Eighteen such patients were identified from an international case registry established to track the investigational use of rFVIIa. The rFVIIa was administered in single or divided doses. Bleeding was reduced in 16 of 18 cases, with total or near complete termination in 9 of 18. Three patients died postoperatively of renal or multiorgan failure, and the others recovered uneventfully. Treatment with rFVIIa has been used before the removal of an intra-aortic balloon pump, for the treatment of refractory bleeding after redo coronary bypass surgery, after aortic valve replacement in a patient with osteogenesis imperfecta, and for intractable bleeding after mitral and tricuspid valve repair.

The use of rFVIIa also has been reported during thyroidec- tomy in a patient with Hermansky-Pudlak syndrome and...
during posterior spinal fusion surgery in 2 children with neuromuscular scoliosis.\textsuperscript{103} The use of rFVIIa has been reported to prevent bleeding during surgery for uncontrollable rectal hemorrhage\textsuperscript{104} and in the management of intractable postsurgical intra-abdominal hemorrhage.\textsuperscript{105} The preoperative use of rFVIIa in 36 patients undergoing prostate surgery was reported to reduce blood loss and the need for blood transfusion.\textsuperscript{106} The use of rFVIIa in orthopedic procedures has been reported as well, such as in total hip arthroplasty in a patient with cirrhosis and thrombocytopenia\textsuperscript{107} and in total knee replacement in a patient with hemophilia with high-titer factor VIII inhibitor.\textsuperscript{2} rFVIIa has been used successfully to control bleeding in a preterm infant undergoing exploratory laparotomy for a ruptured umbilical artery\textsuperscript{108} and in the surgical resection of a massive pseudotumor in a patient with a high-titer factor VIII inhibitor.\textsuperscript{8}

The use of rFVIIa for urgent neurosurgical treatment of patients with coagulopathy seems promising. In a retrospective review of the medical records of 9 patients with coagulopathy needing urgent neurosurgical intervention for various indications, post-rFVIIa coagulation parameters obtained as early as 20 minutes after the infusion of the medication showed normalization of values. No perioperative or postoperative complications were observed.\textsuperscript{109,110}

### Trauma

rFVIIa has been used to control traumatic bleeding.\textsuperscript{111,112} Life-threatening bleeding associated with trauma that was not corrected by other means was reported to have been controlled effectively with rFVIIa.\textsuperscript{26,27,61,111} Rebleeding following subarachnoid hemorrhage is a major concern, and antifibrinolytic agents have been used to prevent it, but they increase the risk of cerebral ischemia and infarction. An open-label, dose-escalation study was conducted with rFVIIa in 10 patients with subarachnoid hemorrhage.\textsuperscript{113} There was no evidence of cerebral ischemia in 9 of the treated patients; middle cerebral artery branch thrombosis contralateral to the aneurysm developed in the last patient. Data from 2 compassionate use clinical trials using rFVIIa to treat central nervous system bleeding in 18 patients with hemophilia A with high-titer inhibitors and 3 patients with factor VII deficiency showed an overall efficacy of 84% with only 1 death.\textsuperscript{114} No major adverse effects were reported.

Massive pulmonary hemorrhage secondary to trauma in a 44-year-old man, which was uncontrolled with standard treatment, was controlled successfully with rFVIIa.\textsuperscript{115} In another case, rFVIIa was used successfully to control massive hemoptyis in acute leukemia.\textsuperscript{116}

### Disseminated Intravascular Coagulation

The use of rFVIIa was reported in a pregnant woman with DIC in whom severe intra-abdominal bleeding developed after cesarean section. rFVIIa was given after an initial attempt to control bleeding with FFP, fibrinogen, platelets, and surgery. Bleeding was controlled rapidly, with resolution of the coagulopathy.\textsuperscript{35}

Another report on the use of rFVIIa in 3 children with bleeding secondary to liver failure and DIC states that bleeding was controlled effectively and the PT was shortened.\textsuperscript{3} Cases 1 and 2 (girls aged 3 and 6 years, respectively) were diagnosed with dengue hemorrhagic fever and prolonged shock. Case 3 (a boy aged 9 months) underwent left lobe hepatectomy for hepatoblastoma, during which 60% of his liver was removed. This case was complicated by myoglobinuria, liver and renal impairment, and early DIC. All 3 patients had active bleeding. The children in cases 1 and 2 received rFVIIa combined with other blood component replacements, while the boy in case 3 received rFVIIa as the only hemostatic agent. A bolus of 40 to 180 µg/kg of body weight was administered, followed by 16.5 to 33 µg/kg of body weight per hour in a continuous infusion. As a result, bleeding was controlled, the PT was shortened, and the factor VII clotting activity was increased significantly.

In another case report, rFVIIa effectively controlled bleeding associated with severe necrotizing pancreatitis.\textsuperscript{117}

### Pharmacokinetics and Dosing of rFVIIa

The pharmacokinetic profiles of rFVIIa have been evaluated in healthy adult volunteers who were pretreated with acenocoumarol, in adults and children with hemophilia A or B, and in adults with cirrhosis and a prolonged PT. The clearance and half-life values of rFVIIa after bolus injections were in the same range in the adult populations studied. The volume of distribution at steady state was slightly smaller in healthy volunteers than in patients with hemophilia. The pharmacokinetic profile of rFVIIa seems to be independent of bleeding or nonbleeding conditions in adults with hemophilia. The values of clearance also were dose-independent in adults with hemophilia and in patients with cirrhosis, whereas in the pediatric patients, the half-life was shorter and clearance was higher than in adults with hemophilia.\textsuperscript{118}

A double-blinded, placebo-controlled, randomized, dose-escalation trial was conducted to investigate 8 single intravenous doses of FFR-rFVIIa (inactivated rFVIIa) in 62 healthy male volunteers. Safety, pharmacokinetics, and pharmacodynamics of FFR-rFVIIa were assessed. The mean elimination half-life ranged from 3.8 to 5.8 hours. The mean area under the curve increased with increasing dose levels.
The maximum concentration seemed to be proportional to the dose level, with the exception of the lowest dose level. A dose-dependent prolongation of the PT was found, demonstrating that FFR-rFVIIa inhibited coagulation via the TF-dependent pathway. FFR-rFVIIa was well tolerated at all dose levels studied.119 The standard dosing has been 90 to 120 µg/kg every 2 to 3 hours until bleeding stops.120

Continuous Infusion of rFVIIa

The standard modality of administration of rFVIIa is intermittent infusion every 2 to 6 hours. rFVIIa has a short half-life, only 2.5 hours, and necessitates frequent dosing intervals to maintain the levels.121 Hence, continuous infusion seems to be more effective for maintaining rFVIIa levels. Continuous infusion of rFVIIa was first described in 1996. It has been mostly used in the treatment of hereditary or acquired hemorrhagia. Compared with bolus dosing, it is more convenient and less expensive; potential pitfalls are hemostatic response and high responding inhibitors and 3 patients with nonhemophilic inhibitors. A satisfactory hemostatic response was achieved in 30 of 35 treatment courses. These findings are comparable with those in other published series using bolus administration of rFVIIa.128,129 In contrast, the results with continuous infusion of rFVIIa in 8 patients with inhibitors to factor VIII undergoing elective surgery were disappointing. Effective hemostasis was achieved in 1 of 2 minor procedures and in 2 of 6 major operations.130 The different outcomes observed in the 2 studies might be explained partly by the differences in the treatment intensity, but there might be other patient-specific variables that might affect the clinical responses to rFVIIa.124

Monitoring of rFVIIa

Laboratory monitoring of hemostatic efficacy in patients treated with rFVIIa is complex. Standard PT and aPTT have limitations and do not correlate with the clinical picture. Factor VII activity assays were used in the past to monitor rFVIIa activity. A modified version of the Staclot VIIa-rTF assay (Diagnostica Stago, Asnieres, France) has been developed that is suitable for monitoring treatment with rFVIIa at low concentrations.131

A thromboelastogram is done on an automated instrument that demonstrates changes occurring during blood coagulation and fibrinolysis. Thromboelastography was evaluated to be better than aPTT as a monitor of hemostatic effects when using rFVIIa.132 Whole blood elasticity as measured by thromboelastography has been shown to improve following rFVIIa therapy. In vivo and ex vivo rotating thromboelastography measurements showed that rFVIIa shortened whole blood clotting time, although normalization did not occur. The efficacy of these principles needs to be tested further.129

A study comparing factor VII activity and rFVIIa assays for 24 patients who received rFVIIa treatment showed a good correlation (r = 0.91), but the values for factor VII activity were 1.63 times higher than those for the rFVIIa method and a relatively wide margin in the interval of the factor VII/rFVIIa ratio was obtained. Cid et al133 believe that the rFVIIa assay would be more suitable for the monitoring of rFVIIa treatment because the factor VII assay has wide interlaboratory variability.

The effect of rFVIIa on the PT was compared with the effect of a standard volume of FFP in preterm neonates with prolonged PTs. The PT remained lower in the rFVIIa group (P = .01) at 3 hours than in the FFP group; the differences at 6 and 12 hours were statistically insignificant.134

Side Effects

Laboratory, animal, and human studies have demonstrated the thrombogenicity of rFVIIa.135,136 Several case reports already have been described in the preceding sections. Acute myocardial infarction was reported in a patient with
hemophilia A and inhibitors after receiving rFVIIa for dental extraction, which shows that transfusion of rFVIIa might promote thrombotic complications, although the thrombogenic potential of rFVIIa is much less than that of activated PCCs. Rosenfeld et al138 described a patient with severe hemophilia A and factor VIII inhibitors in whom pulmonary embolism developed following sequential treatment with activated PCC and rFVIIa. As mentioned earlier, in 1 of 3 patients with Glanzmann thrombasthenia treated with rFVIIa, severe thromboembolic complication developed 5 days after discontinuing rFVIIa treatment. A single institutional report on the use of rFVIIa in 16 patients during a 2-year period recorded 2 thrombotic events following the administration of rFVIIa.140

A study of 54 cases of retinal venous occlusion (RVO) showed that factor VIIa levels were significantly higher in the RVO group than in the control group. There was no significant difference in the factor VIIa levels between the central RVO group and the branched RVO group. Hypertension was highly prevalent in cases of branched RVO. These findings suggest that elevated levels of factor VIIa might have a role in the pathophysiology of central and branched RVO.141

When used in coagulation and platelet disorders, rFVIIa is associated with few side effects. As of November 2000, in an estimated 4,500 patients treated, 5 episodes of DIC, 7 episodes of myocardial infarction, 4 incidents of cerebrovascular ischemia or infarction, 5 episodes of deep vein thrombosis, and 1 episode of intestinal gangrene have been reported, and most of these cases had apparent comorbid or predisposing factors.142

Caution should be exercised when using rFVIIa in patients with underlying conditions that might predispose them to thrombosis and DIC, including crush injury, septicemia, atherosclerotic diseases, and advanced age.

**Discussion**

There has been an increased use of rFVIIa in patients with severe bleeding. This review has attempted to reference most of the reports describing the use of rFVIIa in nonhemophilic conditions, excluding those with acquired inhibitors of factor VIII or IX. There are questions about the indications for this therapy, and some want to use rFVIIa only after attempts to control hemorrhage with conventional factors and blood replacement have failed.

Some reports have described concurrent treatment with antifibrinolytic agents, and some have not. Most have used doses of approximately 90 µg/kg given as an intravenous bolus and have given a second treatment if bleeding persisted, but higher doses might be tolerated. Some reports have described the use of continuous infusion.

In many cases, the PT and aPTT have been shortened markedly after treatment with rFVIIa, and there are few reports of systemic thromboses. In cases in which the fibrinogen level or platelet count is low, it might be best to give these components before administering rFVIIa to optimize the hemostatic effect of the treatment. Recently, rFVIIa has been found to reduce the intraoperative blood loss during resection of congenital vascular lesions (M.W., oral communication, July 2003). At least 2 patients in this series would not have been able to undergo operation without rFVIIa.

Because some uses are in unusual and rare cases, there might never be enough cases to statistically evaluate the effectiveness of rFVIIa, and good clinical judgment will have to be used to determine when to use this agent and how to administer it. This is a new agent in our armamentarium for the treatment of acute hemorrhage.

**References**

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15. Hedner U. NovoSeven as a universal haemostatic agent.


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[DOI: 10.1309/D0G0C96V05CJ5B4J]