

The use of recombinant factor VIIa in the treatment of bleeding disorders

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Recombinant factor VIIa was initially developed for the treatment of hemorrhagic episodes in hemophilic patients with inhibitors to factors VIII and IX. After its introduction, it has also been used “off-label” to enhance hemostasis in non-hemophilic patients who experience bleeding episodes not responsive to conventional therapy. Evidence so far indi-

cates that the use of factor VIIa in hemophilic patients with inhibitors is both safe and effective. Anecdotal reports also suggest that the product is safe and effective in controlling bleeding in nonhemophilic patients. However, its use in these conditions has not been approved by the FDA, and conclusive evidence of its effectiveness from controlled clinical trials is not

yet available. Several questions pertaining to the use of factor VIIa require further investigation, including the mechanism of action; the optimal dose; definitive indications; ultimate safety; and laboratory tests for monitoring therapy. (Blood. 2004;104:3858-3864)

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Introduction

Prothrombin complex concentrates (PCCs), containing prothrombin and factors VII (fVII), IX, and X, were initially developed for treatment of hemophilia B (factor IX deficiency). These concentrates were known to contain small amounts of activated factors, particularly factors VIIa, IXa, and Xa. Their presence led to the use of PCCs in hemophilic patients with inhibitors to factors VIII or IX with the idea that the activated factors might provide a way to “bypass” the need for factor VIII or IX and represent a new approach to the treatment of inhibitors.¹

A clinical trial of the effectiveness of PCCs compared with an albumin placebo was carried out in 1980 and showed that PCCs were significantly more effective in controlling bleeding in hemophilic patients with inhibitors than an albumin placebo.² On the other hand, replacement therapy with factor VIII for similar bleeding episodes in noninhibitor hemophilia patients was virtually 100% effective. Thus, very early on it was known that the term “inhibitor bypassing agent” actually described partial rather than complete effectiveness.

The effectiveness of PCCs in hemophiliacs with inhibitors raised the question as to which component(s) of PCCs was effective as a hemostatic agent. As early as 1975, it was noted that concentrates with higher amounts of factor VII seemed to be more effective than those with lower concentrations of this factor. However, the idea that factor VII or factor VIIa alone might be an active component in PCCs was not pursued at that time.

Since activated factors in PCCs were thought to be responsible for the hemostatic effect, “activated PCCs” were prepared commercially. Autoplex (Baxter Bioscience, Glendale, CA) and FEIBA (factor 8 inhibitor bypassing agent) (initially prepared by Immuno, Vienna, Austria, but now by Baxter Bioscience) were prepared by so-called “controlled activation” of the original “unactivated” prothrombin complex concentrates.³ In clinical trials, the activated PCCs were equal to or marginally better than the original PCC preparations, though the active ingredients remained unknown.^{3,4}

Factor VIIa was considered by several investigators to be a candidate for the major bypassing agent.⁵ In 1981, Kingdon and Hassel injected Autoplex, which contained several activated factors, into a hemophilic dog in which bleeding was induced by a standardized surgical incision on the gum.⁶ This treatment was found to be partially effective in establishing hemostasis in these animals. Although several investigators suspected that factor VIIa possessed bypassing activity, it remained for Hedner and Kisiel to clearly establish the effectiveness of factor VIIa as a hemostatic agent in humans.⁷ They purified factor VII from human plasma under sterile conditions. During preparation, factor VII was activated to factor VIIa. The first preparation was administered to 2 hemophilic patients who had high-titer-factor VIII antibodies and who were experiencing bleeding episodes.⁷ Bleeding in both patients was controlled by the administration of plasma-derived factor VIIa. Subsequently, plasma-derived factor VIIa was observed to be effective in controlling hemorrhage in other hemophilic patients with inhibitors.⁸ The difficulty in preparing factor VII from plasma resulted in a shortage of starting material that precluded extensive use of plasma-derived factor VIIa. The problem of availability was solved by the development of recombinant factor VIIa (rfVIIa) by Novo Nordisk Pharmaceuticals (Bagsvaerd, Denmark).

Preclinical studies with recombinant factor VIIa

Prior to use in human subjects, recombinant factor VIIa was administered to hemophilia A and B dogs subjected to a standardized toenail bleeding time, which was used as an in vivo measure of thrombin generation. Dogs with severe hemophilia A were given the recombinant product in doses ranging from 50 to 220 μg per kg/body weight (BW).⁹ The bleeding time in these dogs was

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normalized except in one animal, which was given the lowest dose of the factor. Similar success was observed in dogs with hemophilia B.⁹ Hemostasis in dogs homozygous for von Willebrand disease (VWD) was not achieved even at higher doses of factor VIIa, suggesting early on that platelet adhesion and aggregation were necessary for the full action of rfVIIa.⁹ Unlike humans, canine platelets do not contain von Willebrand factor (VWF).

Pharmacokinetic studies of recombinant factor VIIa in humans

Pharmacokinetic studies in adults revealed a circulating half-life ($T_{1/2}$) of rfVIIa to be 2.60 to 2.84 hours that was independent of dose.¹⁰ The recovery was slightly less in bleeding versus nonbleeding patients. In the pediatric age group the $T_{1/2}$ was 1.32 hours, significantly shorter than that seen in adults. The clearance rate was also more rapid in children at 67 mL per kg/h, suggesting that higher doses of factor VIIa might be required in the pediatric age group.¹¹

Mechanism of action of factor VIIa

The mechanism of action of fVIIa is controversial, but there is general agreement on several points. It is generally agreed that about 1% of circulating factor VII in healthy individuals is in the activated form and that the amount of the factor VIIa required for “bypassing activity” is much larger than this.¹²⁻¹⁵ It is also generally agreed that the tissue factor (TF) pathway must be intact for fVIIa to have an effect.^{14,16,17} The major disagreement appears to revolve around the issue of whether rfVIIa has any effect independent of tissue factor.¹⁷ One group has developed a cell-based model system of coagulation to study the mechanism of action of fVIIa. In this system, all the plasma procoagulants and relevant inhibitors are added to tissue factor-bearing cells and unactivated platelets in microtiter wells in which coagulation is initiated by addition of fVIIa and calcium.¹⁸ Factor VII and fVIIa are equally effective at initiating the process.¹⁹ In this system, platelet activation occurs first, followed by a burst of thrombin generation. The model system can also be used to mimic the hemophilic condition by omission of factor VIII or IX. A schematic representation of the normal and hemophilic conditions are shown in Figure 1A-B. In the absence of factor VIII or IX it can be shown that at pharmacologic doses, fVIIa will bind weakly to activated platelets and can directly activate factor X to factor Xa such that in the presence of factor V, thrombin generation can be improved over and above that generated by the tissue factor/VIIa complex alone (Figure 2).²⁰⁻²² The binding of rfVIIa to activated platelets may explain why rfVIIa is localized only to the site of bleeding. In this model, it is clear that the tissue factor pathway must be intact in order for the initial activation of platelets to occur by the small amount of thrombin formed at the level of the tissue factor-bearing cell. In addition, the cell-based model system predicts that there is a dose response relationship between fVIIa and thrombin generation. As can be seen in Figure 2, increasing doses of rfVIIa can increase thrombin generation in this system, even in the absence of either factor VIII or factor IX. However, thrombin generation in this system is not completely normalized even at higher rfVIIa concentrations.

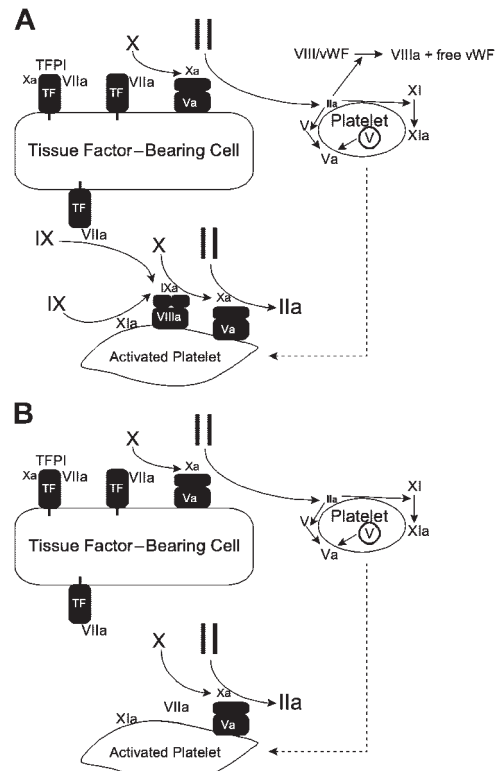


Figure 1. Models of coagulation and hemophilia. (A) Coagulation is initiated when coagulation proteins and platelets come into contact with the extravasculature. Factor VII binds to tissue factor, is activated, and activates both factor IX and factor X. The factor Xa forms a complex with factor Va on the tissue factor-bearing cell and activates a small amount of thrombin. This thrombin acts to amplify the initial coagulation signal by activating platelets causing release of factor V, activating factor XI, cleaving factor VIII and releasing it from VWF, and activating factor XI. In the propagation phase, factor IXa, formed by factor VIIa/tissue factor or generated on the platelet surface by factor XIa, forms a complex with factor VIIIa to activate factor X on the platelet surface where, in complex with factor Va and in the presence of prothrombin, it is protected from inhibition. Formation of the factor Xa/Va complex results in a burst of thrombin generation. (B) In hemophilia, the initiation and amplification phases proceed normally. The propagation phase is absent or significantly decreased because factor Xa cannot be generated on the platelet surface. High-dose factor VIIa acts to partially restore platelet surface factor Xa generation so that factor Xa/Va complex formation proceeds and the propagation phase is improved relative to the hemophilic state.

By contrast, Mann and colleagues²³⁻²⁶ hold the view that the mechanism of action of factor VIIa is dominated by the tissue factor-mediated activity with only a minimal, if any, contribution from TF-independent fVIIa activity. In studies using TF incorporated into lipid vesicles, van't Veer et al observed that fVIIa overcomes the inhibitory effect of zymogen fVII on thrombin generation.^{23,24} While the influence of rfVIIa is dependent on TF, Butenas et al observed that phospholipids or platelets substantially increase the hemostatic potential of rfVIIa.^{25,26}

Lisman and De Groot have recently analyzed the alternative mechanisms of action of rfVIIa.¹⁵ They conclude that the tissue factor pathway is required for rfVIIa to act and that at pharmacologic doses, rfVIIa will also bind to activated platelets and directly activate fX to fXa as suggested by the Roberts group.¹²⁻¹⁴ Lisman et al have also observed that the enhanced thrombin generation from fVIIa not only accelerates clot formation, but also inhibits fibrinolysis by activation of thrombin activatable fibrinolytic inhibitor (TAFI) in factor VIII-deficient plasma.²⁷

Whatever the mechanism of action, it appears that the action of rfVIIa is localized to the site of bleeding since systemic coagulation,

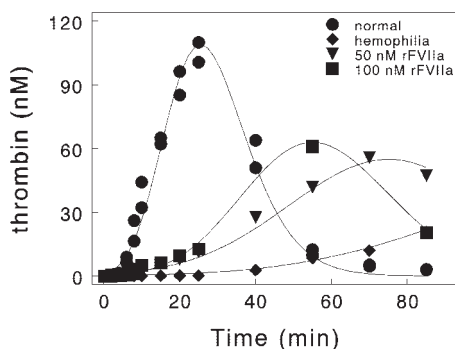


Figure 2. Factor VIIa increases platelet surface thrombin generation. With normal levels of the coagulation proteins (●), the pattern of thrombin generation shows a short lag phase, during which platelets are activated and the coagulation complexes assemble on the activated platelets. This is followed by a burst of thrombin generation that reaches a substantial peak value. The thrombin is ultimately inhibited by antithrombin. In hemophilia (◆), the lag is extended due to slow formation of the factor Xa/Va complex on the platelet surface. There is a weak burst of thrombin generation with a low peak value. Factor VIIa (▼) enhances factor X activation so that factor Xa/Va complexes form more rapidly on the platelet surface. This leads to a shorter lag with an enhanced burst of thrombin leading to a higher peak. Increasing the factor VIIa concentration (■) further shortens the lag, enhances the burst, and leads to an even higher peak of thrombin generation.

if it occurs, appears to be minimal despite the administration of large doses of the factor, even in people without coagulopathy.

Dosage of recombinant factor VIIa

Due to the lack of a specific laboratory test to monitor the effect, initial doses of rFVIIa were chosen on the basis of subjective evaluation of the patient's response. In a randomized double-blind trial of 35 and 70 μg per kg/BW, carried out in 84 subjects with hemophilia A and B with and without inhibitors, it was found that both doses of rFVIIa were about 70% effective in patients with hemarthroses and soft tissue bleeding.²⁸ The mean number of doses required to achieve a subjective response was about 3 for both dose regimens with doses given every 2 to 3 hours. However, in a later prospective randomized trial in hemophilia patients with inhibitors undergoing elective surgery, 35 and 90 μg recombinant factor VIIa were administered. This study showed that the higher dose was more effective than the lower dose.²⁹ More recently, however, doses of 120 μg per kg/BW have been used routinely.³⁰ Given the short T1/2 of factor VIIa, doses have been administered intravenously every 2 hours for the first 48 hours and every 2 to 6 hours for the next 72 hours in nonsurgical cases. Achievement of hemostasis has varied, but in later studies up to 90% of patients have responded to 90 to 120 $\mu\text{g}/\text{kg}$ doses during the first 48 hours.³¹ Even though the recommended dose is 90 $\mu\text{g}/\text{kg}$, it is clear that the optimal dose and dosing intervals of factor VIIa have not been established with certainty. Recent developments suggest that doses higher than those recommended may be more efficacious in patients with hemophilia and may require dosing at less frequent intervals.^{32,33}

Constant infusion regimens for the use of rFVIIa have also been described and have been used successfully.³⁴ With this regimen it may be possible to use less rFVIIa when compared with treatment regimens using bolus doses. However, the continuous infusion regimen is currently not in wide use. When rFVIIa is given as a constant infusion, the peak of thrombin generation is thought to be lower than that seen with bolus doses of rFVIIa.³⁵

Using the cell-based model of coagulation to mimic in vivo coagulation conditions, it was shown that increasing doses of factor

VIIa resulted in increased thrombin generation as shown in Figure 2. In an attempt to increase thrombin generation, these studies led to the use of higher than the recommended doses of rFVIIa for hemophilic patients. In one of the earlier case reports, a 14-year-old patient with hemophilia B who developed a target joint in the left elbow did not respond to the usual doses of factor VIIa but did respond to a dose of 320 μg per kg/BW.³² This dose was given with the knowledge that the T1/2 of factor VIIa in the patient was 1.5 hours, with a clearance rate nearly double that of the average adult.

The effectiveness of recombinant factor VIIa at doses of 300 $\mu\text{g}/\text{kg}$ has been tested in 3 young patients with hemophilia A with inhibitors to factor VIII.³³ Of 114 bleeding episodes, 95 responded to a single 300- μg dose of rFVIIa without side effects. The remaining patients responded to subsequent similar doses of rFVIIa. The bolus injection of this mega dose was considered superior to a standard dose or to a constant infusion of regular doses of the product. Although the number of patients in these studies is small, the data suggest that higher doses are not only more effective but are also safe.³³ It has been noted that with higher doses of VIIa, peak thrombin generation is higher and is thought to result in a more stable and less porous fibrin clot.^{36,37}

It has also been reported that sequential therapy with factor VIIa and prothrombin complex concentrates may be more beneficial than factor VIIa alone, suggesting a synergistic effect between the 2 agents.³⁸

The "mega" doses of rFVIIa used in these studies have not been approved by the FDA and represent "off-label" use of the product. Furthermore, these high doses of rFVIIa have not been used extensively in elderly patients and in those who do not have hemophilia.³⁹

Use of recombinant factor VIIa in hemophilia A and B patients with inhibitors to factors VIII and IX, respectively

Recombinant factor VIIa has been approved by the FDA in the United States only for use in hemophilia A and B patients who have inhibitory antibodies against factor VIII or factor IX. In Europe, rFVIIa has been approved not only for hemophilia with inhibitors, but also for postsurgical bleeding, hemophilia home treatment, factor VII deficiency, and Glanzmann thrombasthenia. The recommended dose according to the package insert is 90 μg per kg/BW of recombinant factor VIIa given in bolus doses intravenously. It is recommended that doses be given every 2 hours until bleeding ceases. Response rates have generally been excellent, ranging up to 90% effectiveness in bleeding episodes in patients with inhibitors. The importance of early therapy has been stressed.⁴⁰ As discussed in the previous section, dosage requirements differ depending on the circumstances surrounding a given bleeding episode. Factor VIIa has also proved effective for the home treatment of bleeding episodes in hemophiliacs with inhibitors. In a "home therapy" trial encompassing 56 patients and 827 bleeding episodes, it was found that the product was effective in 90% of cases.⁴¹

Recombinant factor VIIa has also been used to achieve hemostasis for major surgery in hemophilic patients with inhibitors. Again, dose regimens have varied, but using bolus doses, Ingerslev has recommended that patients undergoing major surgery receive 90 to 120 μg per kg/BW every 2 to 3 hours of factor VIIa throughout the first 2 to 3 days following surgery.⁴² On the third and fourth days, dosage intervals may be decreased to every 3 to 4 hours. Thereafter dosage intervals can be decreased to every 4 to 6 hours until about 7 days. If bleeding complications occur after initial hemostasis is achieved, factor VIIa may be given again every 2 hours until

bleeding ceases. In most cases, antifibrinolytic agents are given concomitantly with rfVIIa.⁴²

Failure to respond to rfVIIa may be due to suboptimal dosing. The major problems in using rfVIIa in hemophilia patients are related to dosage, requirement for frequent dosing, and the lack of a quantitative method for monitoring therapeutic effectiveness.

Use of factor VIIa in patients with other hereditary clotting factor deficiencies

Factor VII deficiency

Factor VIIa has also been used successfully to treat patients with factor VII deficiency. Bleeding episodes in these patients have responded to relatively low doses of the product, ranging from 15 to 20 μg per kg/BW every 2 to 3 hours until cessation of bleeding.^{43,44} Major surgery has also been carried out in factor VII-deficient patients under cover of rfVIIa. Only one factor VII-deficient patient has developed anti-factor VII antibodies after treatment with rfVIIa.⁴⁵

Factor XI deficiency

Recombinant VIIa has also been used to treat patients with factor XI deficiency either with or without inhibitors to factor XI.⁴⁶ Doses of 90 to 120 $\mu\text{g}/\text{kg}$ every 2 to 3 hours until bleeding ceases have been found to be effective in this condition, but the optimal dose has not been clearly defined. Some investigators now consider rfVIIa to be the treatment of choice in factor XI deficiency and for inhibitors to factor XI.

von Willebrand disease (VWD)

There are anecdotal reports of the successful use of the product in stopping bleeding in humans with von Willebrand disease, including type III.⁴⁷ Factor VIIa has been used in those patients who do not respond to conventional therapy because of antibodies to von Willebrand factor (VWF) or due to other complications such as angiodysplasia. Bleeding resulting from oral surgery and angiodysplasia in type III VWD, complicated by an alloantibody against VWF, reportedly responded to bolus infusion of rfVIIa.⁴⁸ Some of these patients also received antifibrinolytic agents as well as von Willebrand factor products.

Use of factor VIIa in platelet disorders

Glanzmann thrombasthenia

There are anecdotal reports of the use of factor VIIa for the treatment of bleeding episodes in patients with Glanzmann thrombasthenia, mostly in those patients who have become unresponsive to platelet transfusions because of the development of alloantibodies to glycoproteins (GPIIb/IIIa). Many of these cases have been reported by Poon et al, who have established a registry of the use of factor VIIa in patients with congenital platelet disorders.⁴⁹ Recombinant VIIa given in doses ranging from about 70 to 100 $\mu\text{g}/\text{kg}$ every 2 hours until bleeding stops has been effective in controlling bleeding in many cases of Glanzmann thrombasthenia. In one series of patients, the use of factor VIIa was reported to be effective in about 48% of patients.⁵⁰

Bernard-Soulier syndrome

Factor VIIa has also been used successfully in Bernard-Soulier syndrome by a few patients unresponsive to platelet transfusion or desmopressin (DDAVP).⁵¹ Factor VIIa has also been reported to be successful in the treatment of hemorrhages in a patient with the Hermansky-Pudlak syndrome.⁵² More experience is necessary before the efficacy of fVIIa can be clearly established in patients with congenital thrombocytopathy.

Thrombocytopenia

In anecdotal reports, bleeding in patients with thrombocytopenia who have not responded to conventional therapy have responded to rfVIIa in doses of 50 to 100 μg per kg/BW. There are reports that the bleeding time was reduced in more than 50% of the patients, and in the majority of cases, bleeding was controlled.^{53,54} For factor VIIa to be effective in patients with thrombocytopenia, the minimal platelet count should be in the range of 5000 to 30 000/ μL . More data are needed before one can adequately assess the efficiency of rfVIIa in thrombocytopenic disorders, although initial reports appear promising.

Use of factor VIIa in other medical conditions

Recombinant factor VIIa has been used for routine bleeding that has failed conventional therapy in a large number of medical disorders. Many of the reports are anecdotal and represent off-label use of the product. Several trials of rfVIIa are ongoing, including prophylaxis for hemophilia with inhibitors, treatment of bleeding after spinal surgery, and orthotopic liver transplantation. There are completed clinical trials for use of rfVIIa in intracranial hemorrhage and in bleeding associated with trauma, but official results from these trials are not yet available. A trial for use of rfVIIa to control bleeding in cardiopulmonary bypass is planned. In the following paragraphs, some of the more common uses of rfVIIa in bleeding problems secondary to medical conditions will be discussed.

Liver disease

Factor VIIa has been used for bleeding in patients with liver disease, including patients who have experienced variceal bleeding from the esophagus and stomach.^{55,56} Doses have varied, ranging from 5 to 120 μg per kg/BW.⁵⁷ The response to infusion of rfVIIa has varied, but in one single-center study, 10 patients with alcoholic cirrhosis and esophageal bleeding were given 80 μg rfVIIa and observed over a 12-hour period. Bleeding was controlled immediately after treatment and lasted for 12 hours in 5 patients. Factor VIIa has been used prophylactically in patients undergoing laparoscopic liver biopsy.⁵⁸ Reports indicate that at least 74% of patients treated with factor VIIa have maintained hemostasis.

In one controlled trial, a total of 245 patients with cirrhosis and gastrointestinal hemorrhage were treated with 8 doses of rfVIIa at 100 μg per kg/BW or with placebo. The end-point was control of gastrointestinal bleeding within 24 hours after rfVIIa administration. In patients in the Childs-Pugh B and C subgroups, those receiving rfVIIa were most likely to exhibit control of bleeding than patients on placebo. However, patients in the Childs-Pugh A subgroup receiving rfVIIa were similar to those on placebo.⁵⁵

There have been other anecdotal reports of the successful use of rfVIIa in the control of bleeding in patients with liver disease,

but failures as well as recurrent bleeding have been reported. In most patients, rFVIIa has been more effective than plasma therapy alone but plasma replacement was synergistic with rFVIIa.⁵⁷ Factor VIIa has also been used successfully to control bleeding during liver transplantation and during partial hepatectomy in noncirrhotic patients.⁵⁹

Intracranial hemorrhage

Factor VIIa has also been used successfully in patients with intracranial hemorrhage as first reported in hemophilia patients with inhibitors.⁶⁰ However, recent experience suggests that intracranial hemorrhage in patients with normal coagulation may also benefit from early therapy with FVIIa.⁶¹ There is evidence that after intracerebral hemorrhage occurs there is expansion of the hematoma mass in more than 50% of patients for up to 6 hours. These observations suggest that early arrest of hematoma growth would improve outcome, and rFVIIa has been suggested as an agent for early intervention.

Use of rFVIIa for reversal of anticoagulant agents

The administration of rFVIIa to patients with warfarin intoxication results in marked reduction of the prothrombin time in doses ranging from 15 to 90 $\mu\text{g}/\text{kg}$, but perhaps more importantly, rFVIIa enhanced hemostasis in those patients who were experiencing hemorrhage.⁶² Recombinant factor VIIa shortens the prothrombin time (PT), but this is not correlated with cessation of hemorrhage.

It has been suggested that rFVIIa is effective in reversing the effect of low-molecular-weight heparin (LMWH).⁶³ On the other hand, it has shown that rFVIIa does not reverse the anticoagulant effects of low-molecular-weight heparin (LMWH) in rabbits, but the dose of LMWH in this study may have been excessive.⁶⁴ Since it has been shown that rFVIIa will not correct the PT or partial thromboplastin time (PTT) of plasma completely deficient in factor X, it may not reverse the effect of factor Xa inhibitors such as low-molecular-weight heparin if factor Xa was completely inhibited.⁶⁵ It is not known whether rFVIIa will be useful in reversing the effects of argatroban and hirudin.⁶⁶ Factor VIIa has been shown to be effective in reversing the anticoagulant effect of the nematode anticoagulant peptide.⁶⁷

Factor VIIa has also been used in many other medical conditions such as bleeding from renal failure,⁶⁸ factor X deficiency and amyloidosis,⁶⁹ diffuse alveolar hemorrhage,⁷⁰ and bleeding following extensive burns.⁷¹ This list is not exhaustive, and there are hundreds of anecdotal reports on the efficacy of VIIa in controlling hemorrhage in a variety of medical disorders when other measures have failed.⁷¹ However, the product is not always effective in controlling bleeding whether due to inadequate dosing, simple failure of the agent, or to unknown other causes.

Use of rFVIIa in patients following trauma in nonhemophilic patients

One of the first off-label uses of rFVIIa was in a soldier who suffered extensive bleeding following a gunshot wound to the abdomen.⁷² This patient had extensive abdominal surgery to control bleeding and required numerous transfusions of red cells, plasma, cryoprecipitate, and platelets. As a result, he experienced

hemodilution, hypothermia, and a severe coagulopathy characterized by thrombocytopenia, prolonged PT and PTT, and hypofibrinogenemia. In an attempt to control hemorrhage, the patient was given 60 μg per kg/BW of rFVIIa on 2 occasions with subsequent dramatic control of the hemorrhage.⁷²

This amazing result led to a series of anecdotal reports on the use of rFVIIa in uncontrolled bleeding conditions in patients subjected to extensive trauma.⁷³ In one study in patients with massive trauma and a multifactorial coagulopathy, 19 patients were treated with 1 to 3 doses of rFVIIa, and in 15 patients excessive hemorrhage was controlled, sometimes within minutes after administration of rFVIIa.⁷⁴ However, 4 of the 19 patients did not respond to rFVIIa.⁷⁴ Similar results have been observed in other critically ill trauma patients.^{75,76}

Patients with severe acidosis or profound shock seem less likely to respond.⁷⁷ A randomized, placebo-controlled trial of the use of rFVIIa in trauma patients has recently been completed but the results are not yet available.

Use of factor VIIa in surgery

Recombinant FVIIa has also been effective in controlling excessive hemorrhage in patients undergoing cardiac surgery.⁷⁸ In anecdotal reports, administration of 1 to 2 doses of rFVIIa at 90 to 120 μg per kg/BW has resulted in effective hemostasis, again without evidence of systemic activation of the clotting system.⁷⁹ Despite reports of the successful use of rFVIIa, there are reports suggesting that it is not always effective.⁸⁰

FVIIa has been used to arrest bleeding in children with large and disfiguring facial hemangiomas.⁸¹ When used prophylactically in these conditions, blood loss is reduced and the surgical field is relatively bloodless. None of the children has suffered any serious adverse events from administration of rFVIIa.

In a double-blind trial of rFVIIa of healthy patients undergoing prostatectomy, it was found that the administration of 40 $\mu\text{g}/\text{kg}$ rFVIIa reduced blood loss to the extent that the need for transfusion of red cells was eliminated.⁸²

The need for controlled clinical trials that address some of the questions related to indications for rFVIIa, type of surgery, dose, and potential side effects is also recognized. For the most part, except for 2 controlled trials related to the use of rFVIIa in patients undergoing prostatectomy and partial liver resection, reports on the efficacy of rFVIIa for surgical bleeding are anecdotal and represent off-label use of the product.

Safety of factor VIIa

There is continuing concern that factor VIIa may cause thromboembolic side effects largely because it is an activated factor given in doses to raise FVIIa levels more than 1000-fold. Evidence to date, however, suggests that rFVIIa is both safe and effective both in hemophilic and nonhemophilic conditions.

It is likely that the safety of the product is due to its selective location at the site of bleeding. As of early 2004, more than 700 000 doses of factor VIIa have been administered to several thousand hemophilic patients with inhibitors with about a 1% incidence of serious adverse events, including myocardial infarction, stroke, pulmonary embolism, and deep venous thrombosis among others.³⁵ Similar adverse events have been reported in a small number of nonhemophilic patients, but the true incidence is not known. Many

of the thrombotic events have occurred in patients with a predisposition to thrombotic complications such as diabetes mellitus, obesity, cancer, and atherosclerotic cardiovascular disease, and administration of rFVIIa to such patients should be approached with caution. Adverse events have not been related to dose. Although FVIIa has an excellent safety profile, further monitoring of safety both in the hemophilic and nonhemophilic condition is warranted.

screening tests of coagulation does not necessarily reflect clinical effectiveness, which is judged subjectively.

Methods being evaluated for monitoring include thromboelastography, thrombin generation over time, wave form analysis of the PTT, and platelet contractile force.⁸³

Monitoring of recombinant factor VIIa therapy

There currently is no satisfactory laboratory test to monitor the clinical effectiveness of rFVIIa. With hemophilic and nonhemophilic patients, administration of FVIIa results in shortening of prothrombin time and the partial thromboplastin time. The prothrombin time generally shortens to around 7 to 8 seconds except in factor V- or factor X-deficient plasma, suggesting that patients completely deficient in factors V and/or X will not benefit from therapy with this product.⁶⁵ The partial thromboplastin time shortening has been demonstrated to be due to the direct activation of factor X by circulating factor VIIa on the phospholipids used in the partial thromboplastin time test.⁶⁵ Thus, shortening of these 2

Conclusions

There is general agreement that factor VIIa is safe and effective in hemophilia patients with inhibitors. Emerging data from anecdotal reports and completed or ongoing clinical trials suggest that rFVIIa is also effective in a variety of bleeding conditions in nonhemophilic patients. This has led some to use the term "universal" or "general" hemostatic agent. Perhaps the use of this term is unfortunate since rFVIIa is not always effective in all hemorrhagic conditions. However, rFVIIa has been shown to be life saving in some patients experiencing life-threatening hemorrhage. In such cases, the terms universal or general become irrelevant, and use of factor VIIa in such patients seems warranted even in the absence of controlled clinical trials.

References

- Penner J. Prothrombin complex concentrates and coagulation. *Ann Intern Med.* 1976;85:531-532.
- Lusher JM, Shapiro SS, Palascak JE, Rao AV, Levine PH, Blatt PM. Efficacy of prothrombin-complex concentrates in hemophiliacs with antibodies to factor VIII: a multicenter therapeutic trial. *N Engl J Med.* 1980;303:421-425.
- Sjamsodin LJ, Heijnen L, Mauser-Bunschoten EP, et al. The effect of activated prothrombin-complex concentrate (FEIBA) on joint and muscle bleeding in patients with hemophilia A and antibodies to factor VIII: a double-blind clinical trial. *N Engl J Med.* 1981;305:717-721.
- Lusher JM, Blatt PM, Penner JA, et al. Autoplex versus proplex: a controlled, double-blind study of effectiveness in acute hemarthroses in hemophiliacs with inhibitors to factor VIII. *Blood.* 1983;62:1135-1138.
- Hedner U, Nilsson IM, Bergentz SE. Studies on the thrombogenic activities in two prothrombin complex concentrates. *Thromb Haemost.* 1979;42:1022-1032.
- Kingdon HS, Hassell TM. Hemophilic dog model for evaluating therapeutic effectiveness of plasma protein fractions. *Blood.* 1981;58:868-872.
- Hedner U, Kisel W. Use of human factor VIIa in the treatment of two hemophilia A patients with high-titer inhibitors. *J Clin Invest.* 1983;71:1836-1841.
- Hedner U, Bjoern S, Bernvil SS, Tengborn L, Stigendahl L. Clinical experience with human plasma-derived factor VIIa in patients with hemophilia A and high titer inhibitors. *Haemostasis.* 1989;19:335-343.
- Brinkhous KM, Hedner U, Garris JB, Diness V, Read MS. Effect of recombinant factor VIIa on the hemostatic defect in dogs with hemophilia A, hemophilia B, and von Willebrand disease. *Proc Natl Acad Sci U S A.* 1989;86:1382-1386.
- Lindley CM, Sawyer WT, Macik BG, et al. Pharmacokinetics and pharmacodynamics of recombinant factor VIIa. *Clin Pharmacol Ther.* 1994;55:638-648.
- Erhardtson E. Pharmacokinetics of recombinant activated factor VII (rFVIIa). *Semin Thromb Hemost.* 2000;26:385-391.
- Monroe DM, Hoffman M, Allen GA, Roberts HR. The factor VII-platelet interplay: effectiveness of recombinant factor VIIa in the treatment of bleeding in severe thrombocytopenia. *Semin Thromb Hemost.* 2000;26:373-377.
- Roberts H. Is factor VIIa a general hemostatic agent? *Yes. J Thromb Haemost.* 2004;2:1691-1694.
- Monroe DM, Roberts HR. Mechanism of action of high-dose factor VIIa: points of agreement and disagreement. *Arterioscler Thromb Vasc Biol.* 2003;23:8-9; discussion 10.
- Lisman T, De Groot PG. Mechanism of action of recombinant factor VIIa. *J Thromb Haemost.* 2003;1:1138-1139.
- Lisman T, Leebeek FW, Meijer K, Van Der Meer J, Nieuwenhuis HK, De Groot PG. Recombinant factor VIIa improves clot formation but not fibrolytic potential in patients with cirrhosis and during liver transplantation. *Hepatology.* 2002;35:616-621.
- Butenas S, Brummel KE, Branda RF, Paradis SG, Mann KG. Mechanism of factor VIIa-dependent coagulation in hemophilia blood. *Blood.* 2002;99:923-930.
- Roberts HR, Monroe DM, Oliver JA, Chang JY, Hoffman M. Newer concepts of blood coagulation. *Haemophilia.* 1998;4:331-334.
- Hoffman M, Monroe DM III. The action of high-dose factor VIIa (FVIIa) in a cell-based model of hemostasis. *Semin Hematol.* 2001;38:6-9.
- Hoffman M, Monroe DM III, Roberts HR. Activated factor VII activates factors IX and X on the surface of activated platelets: thoughts on the mechanism of action of high-dose activated factor VII. *Blood Coagul Fibrinolysis.* 1998;9(suppl 1):S61-S65.
- Hoffman M, Monroe DM, Roberts HR. Cellular interactions in hemostasis. *Haemostasis.* 1996;26(suppl 1):12-16.
- Lisman T, Adelmeijer J, Heijnen HF, de Groot PG. Recombinant factor VIIa restores aggregation of alphaIIb beta3-deficient platelets via tissue factor-independent fibrin generation. *Blood.* 2004;103:1720-1727.
- van't Veer C, Golden NJ, Mann KG. Inhibition of thrombin generation by the zymogen factor VII: implications for the treatment of hemophilia A by factor VIIa. *Blood.* 2000;95:1330-1335.
- van't Veer C, Mann KG. The regulation of the factor VII-dependent coagulation pathway: rationale for the effectiveness of recombinant factor VIIa in refractory bleeding disorders. *Semin Thromb Hemost.* 2000;26:367-372.
- Butenas S, Brummel KE, Paradis SG, Mann KG. Influence of factor VIIa and phospholipids on coagulation in "acquired" hemophilia. *Arterioscler Thromb Vasc Biol.* 2003;23:123-129.
- Butenas S, Brummel KE, Bouchard BA, Mann KG. How factor VIIa works in hemophilia. *J Thromb Haemost.* 2003;1:1158-1160.
- Thabut D, de Franchis, Bendtsen F, et al. Inhibition of fibrinolysis by recombinant factor VIIa in plasma from patients with severe hemophilia A [abstract]. *J Hepatol.* 2003;38:13.
- Lusher JM, Roberts HR, Davignon G, et al. A randomized, double-blind comparison of two dosage levels of recombinant factor VIIa in the treatment of joint, muscle and mucocutaneous haemorrhages in persons with haemophilia A and B, with and without inhibitors. *rFVIIa Study Group. Haemophilia.* 1998;4:790-798.
- Shapiro A, Gilchrist GS, Hoots WK, Gastineau DA. Prospective randomized trial of two doses of rFVIIa (Novoseven) in hemophilic patients with inhibitors undergoing surgery. *J Thromb Haemost.* 1998;80:773-778.
- Hedner U. Dosing with recombinant factor VIIa based on current evidence. *Semin Hematol.* 2004;41:35-39.
- Hedner U. Recombinant factor VIIa (Novoseven) as a hemostatic agent. *Semin Hematol.* 2001;38:43-47.
- Cooper HA, Jones CP, Campion E, Roberts HR, Hedner U. Rationale for the use of high dose rFVIIa in a high-titre inhibitor patient with haemophilia B during major orthopaedic procedures. *Haemophilia.* 2001;7:517-522.
- Kenet G, Lubetsky A, Luboshitz J, Martinowitz U. A new approach to treatment of bleeding episodes in young hemophilia patients: a single bolus megadose of recombinant activated factor VII (NovoSeven). *J Thromb Haemost.* 2003;1:450-455.
- Schulman S, d'Oiron R, Martinowitz U, et al. Experiences with continuous infusion of recombinant activated factor VII. *Blood Coagul Fibrinolysis.* 1998;9(suppl 1):S97-S101.
- Abshire T, Kenet G. Recombinant factor VIIa: review of efficacy, dosing regimens and safety in

- patients with congenital and acquired factor VIII or IX inhibitors. *J Thromb Haemost.* 2004;2:899-909.
36. He S, Blomback M, Jacobsson Ekman G, Hedner U. The role of recombinant factor VIIa (rFVIIa) in fibrin structure in the absence of FVIII/FIX. *J Thromb Haemost.* 2003;1:1215-1219.
 37. Wolberg AS, Monroe DM, Roberts HR, Hoffman M. Elevated prothrombin results in clots with an altered fiber structure: a possible mechanism of the increased thrombotic risk. *Blood.* 2003;101:3008-3013.
 38. Key NS, Christie B, Henderson N, Nelsestuen GL. Possible synergy between recombinant factor VIIa and prothrombin complex concentrate in hemophilia therapy. *Thromb Haemost.* 2002;88:60-65.
 39. Roberts HR, Monroe DM III, Hoffman M. Safety profile of recombinant factor VIIa. *Semin Hematol.* 2004;41:101-108.
 40. Lusher J. Acute hemarthroses: the benefits of early versus late treatment with rFVIIa. *Blood Coagul Fibrinolysis.* 2000;11:S45-S49.
 41. Key NS, Aledort LM, Beardsley D, et al. Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (Novoseven) in haemophiliacs with inhibitors. *Thromb Haemost.* 1998;80:912-918.
 42. Ingerslev J. Efficacy and safety of recombinant factor VIIa in the prophylaxis of bleeding in various surgical procedures in hemophilic patients with factor VIII and factor IX inhibitors. *Semin Thromb Hemost.* 2000;26:425-432.
 43. Poon MC. Use of recombinant factor VIIa in hereditary bleeding disorders. *Curr Opin Hematol.* 2001;8:312-318.
 44. Mariani G, Testa MG, Di Paolantonio T, Molskov Bech, Hedner U. Use of recombinant, activated factor VII in the treatment of congenital factor VII deficiencies. *Vox Sang.* 1999;77:131-136.
 45. Bauer KA. Treatment of factor VII deficiency with recombinant factor VIIa. *Haemostasis.* 1996;26(suppl 1):155-158.
 46. Salomon O, Zivelin A, Livnat T, et al. Prevalence, causes, and characterization of factor XI inhibitors in patients with inherited factor XI deficiency. *Blood.* 2003;101:4783-4788.
 47. Ciavarella N, Schiavoni M, Valenzano E, Mangini F, Inchingolo F. Use of recombinant factor VIIa (NovoSeven) in the treatment of two patients with type III von Willebrand's disease and an inhibitor against von Willebrand factor. *Haemostasis.* 1996;26(suppl 1):150-154.
 48. Meijer K, Peters FT, van der Meer J. Recurrent severe bleeding from gastrointestinal angiodysplasia in a patient with von Willebrand's disease, controlled with recombinant factor VIIa. *Blood Coagul Fibrinolysis.* 2001;12:211-213.
 49. Poon MC, D'Oiron R, Von Depka M, et al. Prophylactic and therapeutic recombinant factor VIIa administration to patients with Glanzmann's thrombasthenia: results of an international survey. *J Thromb Haemost.* 2004;2:1096-1103.
 50. Almeida AM, Khair K, Hann I, Liesner R. The use of recombinant factor VIIa in children with inherited platelet function disorders. *Br J Haematol.* 2003;121:477-481.
 51. Peters M, Heijboer H. Treatment of a patient with Bernard-Soulier syndrome and recurrent nosebleeds with recombinant factor VIIa. *Thromb Haemost.* 1998;80:352.
 52. del Pozo Pozo AI, Jimenez-Yuste V, Villar A, Quintana M, Hernandez-Navarro F. Successful thyroidectomy in a patient with Hermansky-Pudlak syndrome treated with recombinant activated factor VII and platelet concentrates. *Blood Coagul Fibrinolysis.* 2002;13:551-553.
 53. Vidarsson B, Onundarson PT. Recombinant factor VIIa for bleeding in refractory thrombocytopenia. *Thromb Haemost.* 2000;83:634-635.
 54. Goodnough LT. Experiences with recombinant human factor VIIa in patients with thrombocytopenia. *Semin Hematol.* 2004;41:25-29.
 55. Thabut D FR, Bendtsen F. Efficacy of recombinant rFVIIa in cirrhotic patients with upper gastrointestinal bleeding: a randomized placebo controlled multicenter trial [abstract]. *Proc Dig Dis Week.* 2003. Abstract 102422.
 56. Ejlersen E, Melsen T, Ingerslev J, Andreassen RB, Vilstrup H. Recombinant activated factor VII (rFVIIa) acutely normalizes prothrombin time in patients with cirrhosis during bleeding from oesophageal varices. *Scand J Gastroenterol.* 2001;36:1081-1085.
 57. Caldwell SH, Chang C, Macic BG. Recombinant activated factor VII (rFVIIa) as a hemostatic agent in liver disease: a break from convention in need of controlled trials. *Hepatology.* 2004;39:592-598.
 58. Bernstein DE, Jeffers L, Erhardtson E, et al. Recombinant factor VIIa corrects prothrombin time in cirrhotic patients: a preliminary study. *Gastroenterology.* 1997;113:1930-1937.
 59. Hendriks HG, Meijer K, de Wolf JT, et al. Reduced transfusion requirements by recombinant factor VIIa in orthotopic liver transplantation: a pilot study. *Transplantation.* 2001;71:402-405.
 60. Veshchev I, Elran H, Salame K. Recombinant coagulation factor VIIa for rapid preoperative correction of warfarin-related coagulopathy in patients with acute subdural hematoma. *Med Sci Monit.* 2002;8:CS98-CS100.
 61. Mayer SA. Ultra-early hemostatic therapy for intracerebral hemorrhage. *Stroke.* 2003;34:224-229.
 62. Deveras RA, Kessler CM. Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate. *Ann Intern Med.* 2002;137:884-888.
 63. Bijsterveld NR, Vink R, van Aken BE, et al. Recombinant factor VIIa reverses the anticoagulant effect of the long-acting pentasaccharide idraparinux in healthy volunteers. *Br J Haematol.* 2004;124:653-658.
 64. Chan S, Kong M, Minning DM, Hedner U, Marder VJ. Assessment of recombinant factor VIIa as an antidote for bleeding induced in the rabbit by low molecular weight heparin. *J Thromb Haemost.* 2003;1:760-765.
 65. Telgt DS, Macic BG, McCord DM, Monroe DM, Roberts HR. Mechanism by which recombinant factor VIIa shortens the aPTT: activation of factor X in the absence of tissue factor. *Thromb Res.* 1989;56:603-609.
 66. Catlett JP, Alving BM. Update in hematology. *Ann Intern Med.* 2002;136:136-143.
 67. Friederich PW, Levi M, Bauer KA, et al. Ability of recombinant factor VIIa to generate thrombin during inhibition of tissue factor in human subjects. *Circulation.* 2001;103:2555-2559.
 68. Moisescu E, Ardelean L, Simion I, Muresan A, Ciupan R. Recombinant factor VIIa treatment of bleeding associated with acute renal failure. *Blood Coagul Fibrinolysis.* 2000;11:575-577.
 69. Boggio L, Green D. Recombinant human factor VIIa in the management of amyloid-associated factor X deficiency. *Br J Haematol.* 2001;112:1074-1075.
 70. Henke D, Falk RJ, Gabriel DA. Successful treatment of diffuse alveolar hemorrhage with activated factor VII. *Ann Intern Med.* 2004;140:493-494.
 71. Bianchi A, Jackson D, Maitz P, Thanakrishnan G. Treatment of bleeding with recombinant factor VIIa in a patient with extensive burns. *Thromb Haemost.* 2004;91:203-204.
 72. Kenet G, Walden R, Eldad A, Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet.* 1999;354:1879.
 73. Martinowitz U, Kenet G, Segal E, et al. Recombinant activated factor VII for adjunctive hemorrhage control in trauma. *J Trauma.* 2001;51:431-438; discussion 438-439.
 74. Martinowitz U, Kenet G, Lubetski A, Luboshitz J, Segal E. Possible role of recombinant activated factor VII (rFVIIa) in the control of hemorrhage associated with massive trauma. *Can J Anaesth.* 2002;49:S15-S20.
 75. Dutton RP HJ, Scalea TM. Recombinant factor VIIa for the control of hemorrhage: early experience in critically ill trauma patients. *Can J Anaesth.* 2003;5:184-188.
 76. Aldouri M. The use of recombinant factor VIIa in controlling surgical bleeding in non-haemophilic patients. *Pathophysiol Haemost Thromb.* 2002;32(suppl 1):41-46.
 77. Meng ZH, Wolberg AS, Monroe DM III, Hoffman M. The effect of temperature and pH on the activity of factor VIIa: implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients. *J Trauma.* 2003;55:886-891.
 78. Tobias JD, Berkenbosch JW, Russo P. Recombinant factor VIIa to treat bleeding after cardiac surgery in an infant. *Pediatr Crit Care Med.* 2003;4:49-51.
 79. Tanaka KA, Waly AA, Cooper WA, Levy JH. Treatment of excessive bleeding in Jehovah's Witness patients after cardiac surgery with recombinant factor VIIa (NovoSeven). *Anesthesiology.* 2003;98:1513-1515.
 80. Dietrich W, Spannagl M. Caveat against the use of activated recombinant factor VII for intractable bleeding in cardiac surgery. *Anesth Analg.* 2002;94:1369-1370; author reply 370-1361.
 81. Waner M. Novel hemostatic alternatives in reconstructive surgery. *Semin Hematol.* 2004;41:163-167.
 82. Friederich P, Heny C, Messelink E, et al. Effects of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double blind placebo controlled trial. *Lancet.* 2003;361:201-205.
 83. Gabriel DA, Carr M, Roberts HR. Monitoring coagulation and the clinical effects of recombinant factor VIIa. *Semin Hematol.* 2004;41:20-24.