

Optimal use of recombinant factor VIIa in the control of bleeding episodes in hemophilic patients

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Abstract: One of the last remaining clinical hurdles in the treatment of people with hemophilia is the development of inhibitors. Alloantibodies or autoantibodies directed at coagulation factors render the infusion of coagulation factor concentrates ineffective, and alternative means must be used to achieve hemostasis. Recombinant factor VIIa (rFVIIa) was developed to control bleeding episodes in hemophilic patients with inhibitors. Clinical efficacy in achieving hemostasis in inhibitor patients was demonstrated by a compassionate-use protocol, as well as in randomized controlled trials. To date, over 1.5 million doses of rFVIIa have been given to inhibitor patients, with an excellent efficacy and safety record. Because of its short half-life, alternative means of dosing and infusing rFVIIa have been explored and are reviewed here.

Keywords: hemophilia, inhibitor, recombinant, factor VIIa, inhibitors

Introduction

Hemophilia is a disorder characterized by recurrent abnormal bleeding, in particular, into muscles and joints. It is caused by a deficiency of various coagulation factors, with hemophilia A caused by factor VIII (FVIII) deficiency, hemophilia B caused by factor IX (FIX) deficiency, and hemophilia C caused by factor XI (FXI) deficiency. Its treatment was revolutionized by the advent of coagulation factor concentrates. These concentrates allow hemophilic patients to receive factor replacement in order to achieve hemostasis during bleeding episodes, and are also used to prevent bleeding episodes.¹ Factor concentrates were initially derived from human plasma. Viral inactivation techniques were not employed with the early-generation coagulation factor concentrates, resulting in the transmission of hepatitis and human immunodeficiency virus infection to hemophilic patients.² Since the mid-1980s, viral inactivation techniques have been used for all coagulation factor concentrates. In addition, recombinant FVIII and later, recombinant FIX concentrates were developed. As a result, there has been no transmission of clinically relevant infectious agents in coagulation concentrates for over 20 years.^{2,3} The last remaining major clinical hurdle in the treatment of hemophilia is the development of inhibitors, ie, an immune response to infused coagulation factors.

People with hemophilia are born with a deficient or absent coagulation factor, and the infusion of a coagulation factor replacement protein is complicated in some patients by the development of an immune response to that protein. The alloantibodies that develop are targeted against the infused coagulation factor and are known as inhibitors. Inhibitor antibodies rapidly inactivate infused coagulation proteins, rendering them ineffective for achieving hemostasis. Overall, 20%–50% of people with hemophilia develop inhibitors.⁴ Fortunately, these inhibitors are usually transient and of little clinical

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significance, but persist in approximately 20% of people with hemophilia A and 1% of people with hemophilia B.^{5,6} In addition, autoantibodies directed against coagulation factors can develop in people with acquired hemophilia. The incidence of acquired hemophilia is approximately 1/1,000,000 per year, with the elderly and people with other immunologic diseases prone to development of the disorder.⁷ Additional measures must be used to achieve hemostasis during bleeding episodes in people with inhibitors.

Bypassing factors VIII and IX

Bypassing agents must be used in order to achieve hemostasis in patients with inhibitors. These agents take advantage of the multiple pathways available to generate a fibrin clot (Figure 1). There are two recognized pathways available to convert fibrinogen to fibrin. Under normal physiologic circumstances, fibrin is not formed unless blood is exposed to tissue factor,

which can bind to either inactive or activated factor VII (FVII). The majority of FVII circulates in an inactive form, but a small percentage circulates in an active form (FVIIa).⁸ The binding of FVIIa to tissue factor creates a complex which can produce activated factor X (FXa). FXa, along with its cofactor, activated factor Va (FVa), can then convert prothrombin into thrombin (IIa), and thrombin can convert fibrinogen into fibrin. This pathway is variously known as the initiation phase, tissue factor, or extrinsic pathway of clot formation. Although this pathway is sufficient to form some fibrin, it does not form a stable fibrin clot under normal physiologic circumstances. This is because the tissue factor pathway is rapidly inhibited by the tissue factor pathway inhibitor (TFPI). In order to form a stable fibrin clot, additional fibrin must be generated by the propagation phase/intrinsic coagulation pathway.⁹ The small amount of thrombin generated by the tissue factor pathway has many functions, one of which is the formation of activated FXI

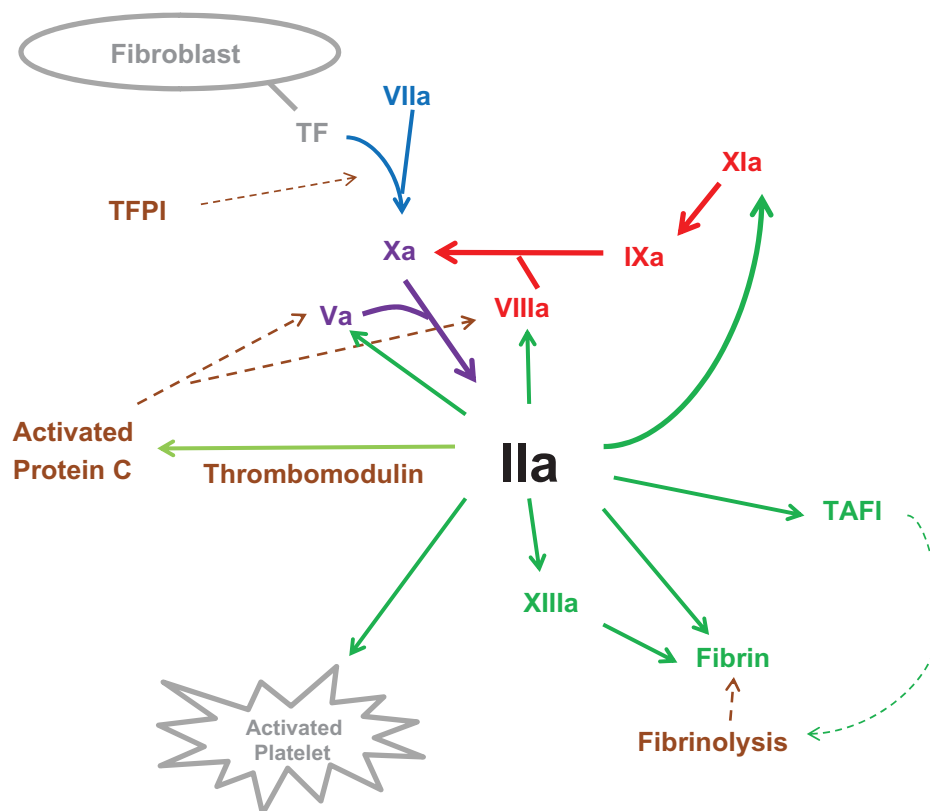


Figure 1 Tissue factor initiated blood coagulation. During the initiation phase, blood becomes exposed to TF-bearing cells. Inactivated Factor VII and VIIa compete for binding with TF. Once the TF: VIIa complex is formed, X is activated to factor Xa. Factor Xa and Va form the prothrombinase complex which converts prothrombin (II) to thrombin (IIa). The nanomolar amount of thrombin generated can activate platelets, Factor V, VIIIa, and XIa. Small amounts of fibrinogen are converted to fibrin by thrombin, but not enough to form a stable clot. The initiation phase is rapidly inhibited by TFPI. In order to form a stable clot, a burst in thrombin activity is required, which occurs through the propagation phase. XIa can activate IXa, with the resulting IXa: VIIIa forming the Xase complex. This complex can form Xa. Additional prothrombinase is formed, which activates thrombin which can feed back and generate more XIa, thus creating a burst in thrombin activity. In addition to generating a sufficient amount of fibrin for stable clot formation, the burst in thrombin activity also generates TAFI which inhibits fibrinolysis. Fibrin is cross-linked by XIIIa, which is activated by thrombin. Solid arrows indicate activation. Dashed arrows indicate inhibition. Blue equals the initiation phase. Red equals the propagation phase. Purple equals both. Green arrows indicate substances activated by thrombin. Brown indicates inhibitors of coagulation.

Abbreviations: TAFI, thrombin-activatable fibrinolysis inhibitor; TF, tissue factor; TFPI, tissue factor pathway inhibitor; VIIa, activated factor VII; X, factor X; Va, factor Va; VIIIa, activated factor VIII; XIa, activated factor XI; IXa, activated factor IX.

(FXIa). FXIa can then generate activated FIX (FIXa). FIXa along with its cofactor, activated FVIII (FVIIIa), forms an Xase (tenase) complex which activates FX (FXa). FXa along with its cofactor, FVa, forms the prothrombinase complex which generates more thrombin which can feed back and generate more FXIa, as well as convert fibrinogen to fibrin.^{8,9} The principal role of the coagulation cofactors, FVIIIa and FVa, is to cause the formation of the Xase and prothrombinase complex on the phospholipid surfaces of cells and platelets. This increases the rate of FXa and thrombin conversion by several orders of magnitude.¹⁰

The positive feedback loop of the propagation phase is necessary for a burst in thrombin generation which is required for the formation of a stable fibrin clot. Patients with hemophilia do not bleed because they cannot generate fibrin, but because they cannot generate the large burst in thrombin necessary to form a stable fibrin clot. Hemophilic patients with inhibitors cannot restore their ability to generate a burst in thrombin by infusions of the deficient coagulation factor because the antibody directed against the coagulation factor renders it inactive. In order to generate the required burst in thrombin activity, one must bypass the intrinsic coagulation cascade and take advantage of the tissue factor pathway.^{8,9}

Prothrombin complex concentrates and factor VIIa

Early attempts at the generation of a FIX complex concentrate in the late 1960s resulted in a concentrate that not only contained FIX, but also factor II (thrombin), FVII, and FX.¹¹ Because factors II, VII, and X are key components of the tissue factor pathway, FIX concentrates known as prothrombin complex concentrate (PCC) were used to treat hemophilic patients with inhibitors.¹¹ An alternative method of treatment was porcine FVIII. Although PCCs were successful in achieving hemostasis in patients with inhibitors, they were not as successful as using specific factor concentrates in noninhibitor patients. This situation was improved by the generation of PCCs in which the coagulation factors were activated. The activated prothrombin complex concentrates (aPCCs) were able to achieve hemostasis in approximately 60% of bleeding episodes in inhibitor patients.¹¹ However, PCCs developed before the mid-1980s were complicated by the transmission of infectious agents, and high doses of PCCs and aPCCs were associated with thrombosis.¹² In addition, the PCCs and aPCCs contain FIX and trace amounts of FVIII, which could lead to an anamnestic response in inhibitor patients.¹²

Several lines of evidence pointed toward FVIIa as the principal bypassing agent in PCCs and aPCCs. Following

an infusion of PCCs in hemophilia B patients, FVII activity rose significantly more than that of FIXa or FXa.¹³ Secondly, the ratio of FVIIa/FVII is high in PCCs and even more so in aPCCs.¹³ This led several investigators, the principal of whom was Ulla Hedner, to suspect that FVIIa alone could bypass the need for FVIII or FIX in order to achieve hemostasis in hemophilic patients with inhibitors. In the early 1980s, Hedner and Kiesel were able to develop a FVIIa concentrate from donated human plasma.¹⁴ They reported on the first successful experience using this agent in two patients with hemophilia and high titer inhibitors in 1983.¹³

Factor VIIa is able to restore the ability of inhibitor patients to generate a burst in thrombin by at least two mechanisms^{9,15} (Figure 2). Infusions of FVIIa increase the relative amount of FVIIa compared with inactive FVII. This increases the likelihood of FVIIa binding to tissue factor, thereby increasing the generation of FXa and thrombin.⁹ This process can still be inhibited by TFPI. Secondly, supraphysiologic concentrations of FVIIa can generate Xa on the surface of activated platelets in a tissue factor-independent fashion. This pathway is not inhibited by TFPI or FVIII/FIX inhibitory antibodies.¹⁵ Via these mechanisms, FVIIa can generate a burst in thrombin without the need for the intrinsic cascade and factors VIII, IX, and XI. In addition, the localization of FVIIa activity to the activated platelet surface reduces the risk of systemic thrombin generation.

The production of FVIIa from human plasma proved to be a cumbersome task, and carried the potential risk of transmission of infectious agents (although viral inactivation processes were being developed by this time).¹⁴ With the advent of molecular biology and genetic engineering, the ability to clone and express genes was being developed. A review of the manufacturing process for rFVIIa (Novoseven[®]) is described by Persson et al¹⁶ and summarized below:

FVII cDNA was cloned from a phage-lambda human cDNA expression library using radio-labeled antibody against FVII. Because FVII undergoes extensive posttranslational modification, a mammalian cell line was required to produce rFVII. A baby hamster kidney cell line was transfected with a plasmid containing the human FVII cDNA and cloned. Working cell lines from the master cell line are then grown in biofermenters in a growth medium containing New Zealand derived calf serum and vitamin K. Medium is then harvested from the biofermenter and rFVII is purified using anion exchange and monoclonal antibody columns. rFVII is autoactivated into rFVIIa during the process of purification. Detergents are added during the purification process to inactivate any enveloped viruses. The current formulation of rFVIIa (Novoseven RT) contains NaCl,

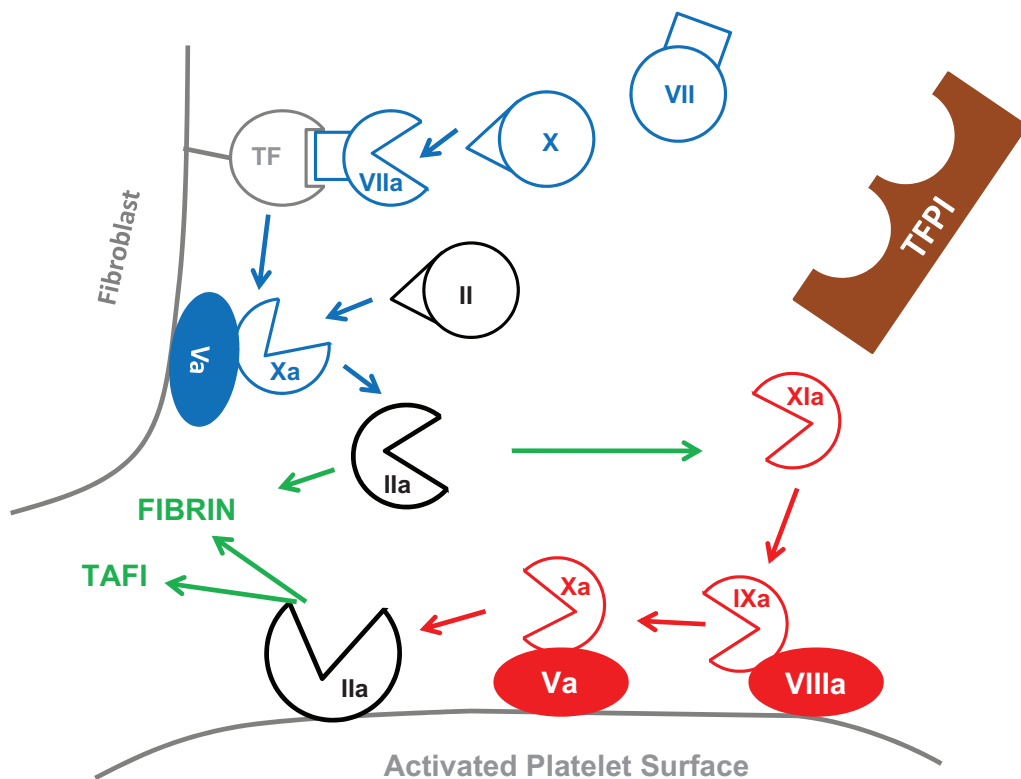


Figure 2a Cell-mediated model of normal coagulation. The TF: VIIa complex forms on a TF-bearing cell. Prothrombinase then forms on this cell membrane to generate thrombin. Additional thrombin is propagated through XIa and the Xase and prothrombinase complexes formed on the surface of activated platelets.
Abbreviations: TF, tissue factor; VIIa, activated factor VII; XIa, activated factor XI.

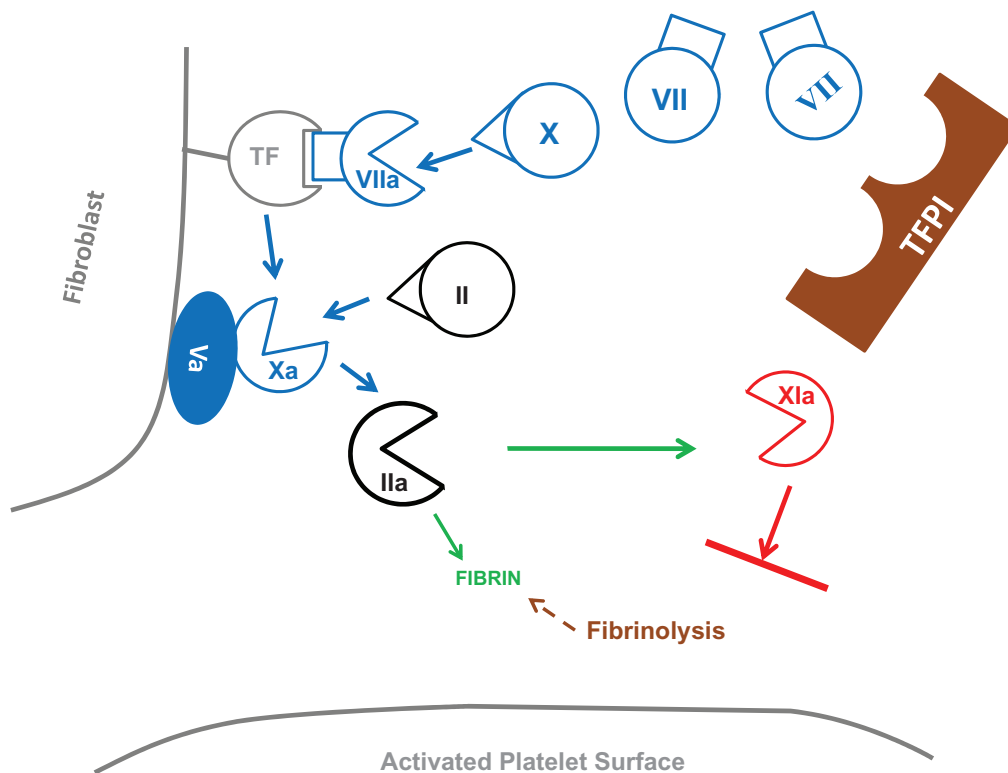


Figure 2b Cell-mediated model in a hemophilic patient with an inhibitor. The TF:VIIa complex and prothrombinase complex can generate thrombin, however the propagation phase cannot occur due to the absence of factors VIII or IX. TFPI rapidly inhibits the TF:VIIa complex.
Abbreviations: TF, tissue factor; VIIa, activated factor VII; TFPI, tissue factor pathway inhibitor.

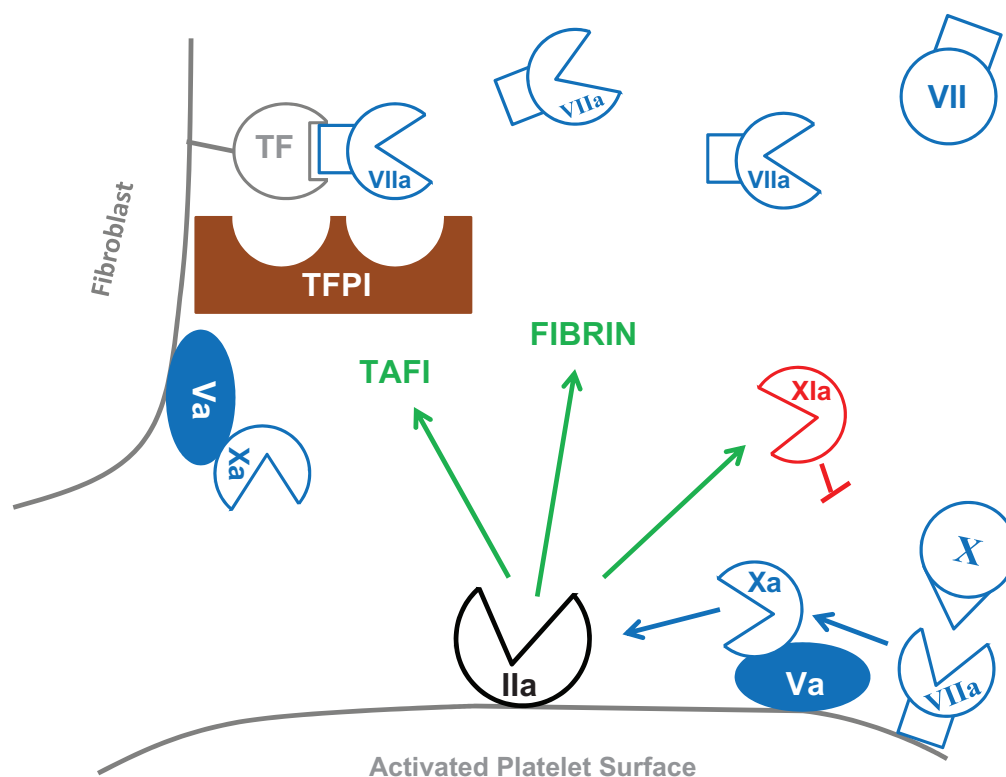


Figure 2c Cell-mediated model with supraphysiologic VIIa. rVIIa can outcompete factor VII for TF binding. Thrombin is generated by the TF:rVIIa complex and prothrombinase as above. This can be inhibited by TFPI. In addition, a burst in thrombin activity is restored by the activation of factor X by rVIIa present on the surface of activated platelets. **Abbreviations:** VIIa, activated Factor VII; rVIIa, recombinant activated Factor VII; TF, tissue factor; TFPI, tissue factor pathway inhibitor.

CaCl₂, glycylglycine, polysorbate 80, mannitol, sucrose, and methionine. After the rFVIIa is formulated, it is dispensed into vials, and freeze-dried.

Pharmacokinetics of rFVIIa

Preclinical studies of rFVIIa in a hemophilic dog model demonstrated the ability of rFVIIa to correct the hemostatic defect in dogs subjected to a standardized bleeding assay.¹⁷ Pharmacokinetic studies of rFVIIa have been hampered by the lack of an assay specific for rFVIIa. As a surrogate, FVII clotting activity has been used. Studies in healthy adult volunteers anticoagulated with acenocoumarol, adult patients with hemophilia A and B, pediatric patients with hemophilia, and patients with cirrhosis were undertaken.^{18,19} The studies revealed a median elimination half-life of 2.45 hours in adults and 1.3 hours in children. The median clearance in adults was 34.5 mL/kg/hour and 67 mL/kg/hour in children. The pharmacokinetic parameters were similar in healthy adult volunteers to those in patients with hemophilia, as well as bleeding and nonbleeding patients. These preclinical and pharmacokinetic studies assisted in the development of appropriate dosing during the clinical trials of rFVIIa. A more recent evaluation of radiolabeled rFVIIa in a

mouse model revealed extensive extravascular accumulation, particularly in the liver and in calcified cartilage.²⁰ This model suggests that rFVIIa may have biologic effects that last much longer than its measurable intravascular half-life.

Clinical studies of rFVIIa

In 1988 Ulla Hedner described the first use of rFVIIa in a patient with congenital hemophilia A and a high titer inhibitor.²¹ rFVIIa was given prior to and following a knee synovectomy. Excellent hemostasis was achieved with a dose of 54 µg/kg, and there were no signs of systemic activation of the coagulation system or other adverse events.²¹ Following this report, a compassionate-use program was put in place and over the next 10 years, at least 400 patients were treated with rFVIIa for bleeding episodes or during surgical procedures.¹² Anecdotal case reports from the compassionate-use program suggested that rFVIIa was effective and safe. There were no anamnestic responses reported. Simultaneously, several controlled clinical studies were undertaken, all of which were published in 1998.^{22–24}

In a study by Lusher et al patients with congenital hemophilia A or B with or without inhibitors were randomized in a blinded fashion to receive rFVIIa at doses of either

35 µg/kg or 70 µg/kg during a joint, muscle, or mucocutaneous bleeding episode.²² The study medication was given at intervals of 2.5 hours until hemostasis was achieved, or a maximum of six doses was given. Response was graded as excellent, effective, partially effective, or ineffective. Overall, 78% and 68% of inhibitor patients with joint bleeds received an excellent or effective score for the 35 µg/kg and 70 µg/kg doses, respectively. The two dosage regimens showed no statistically significant differences in response to joint, muscle, or mucocutaneous bleeding. Both doses were shown to be safe, with no serious adverse events attributable to rFVIIa. Although patients with hemophilia who did not have inhibitors also had a good response to rFVIIa, their response was felt to be inferior to responses with FVIII or FIX concentrates achieved by historic controls. Because patients in this study were required to receive the study medication at a treatment center, there was a considerable time delay between onset of bleeding and the time when the medication was given. To control for this, a home treatment study was conducted.

Key et al described a study using rFVIIa in the home setting.²³ This was an open-label, nonblinded, multicenter, single-arm study in hemophilia A and B patients with inhibitors. Patients received an infusion of rFVIIa 90 µg/kg within eight hours of the onset of a joint, muscle, or mucocutaneous bleed. This dose was chosen based on the results of the compassionate-use program. Patients could receive up to two additional doses spaced three hours apart until an effective response was achieved. An additional maintenance dose of rFVIIa was given three hours after an effective response. Using this regimen, 97% of bleeding episodes were graded as effective or partially effective (92% effective) and hemostasis was maintained for 24 hours in 95% of bleeding episodes. There was one case of superficial phlebitis at the infusion site, otherwise no significant adverse events were attributed to rFVIIa.

A third study investigated rFVIIa in the surgical setting.²⁴ This was a double-blind, randomized, multicenter study of congenital hemophilia A or B patients with inhibitors and nonhemophilic patients with acquired inhibitors undergoing major (n = 11) or minor (n = 18) surgery. Patients were randomized to receive rFVIIa 35 µg/kg or 90 µg/kg prior to surgery and at two-hourly intervals thereafter for 48 hours. After the first 48 hours, the patients received the study medication every 2 to 6 hours for 3 further days. An additional blinded dose was allowed at any time if hemostasis was inadequate. There was no significant difference in intraoperative bleeding or the ability to maintain hemostasis for the first 48 hours postoperatively between the two groups. Virtually all the patients had adequate hemostasis during the first 48 hours.

Over the next three days, significantly fewer patients receiving the 35 µg/kg dose maintained hemostasis, especially those undergoing a major surgical procedure. One patient developed an internal jugular vein thrombosis at the site of a central venous catheter. No other adverse events attributable to the study medications were described.

Based on the results of these studies, rFVIIa was approved in Europe, the US, and Japan for use in patients with congenital or acquired hemophilia and inhibitors. It eventually gained approval for use in over 70 countries worldwide.²⁵ The initial approval recommended a dose of 90 µg/kg given every two hours until hemostasis is achieved, or until the treatment is judged to be inadequate. For surgical procedures, the recommendation is 90 µg/kg given immediately prior to surgery, repeated every two hours for 48 hours, and then repeated at 2- to 6-hour intervals until healing has occurred. Because of the inconvenience of transporting rFVIIa and storing it at 2–8°C, a new formulation of rFVIIa which can be stored at room temperature has become available.²⁵ This formulation is available in 1000, 2000, and 5000 µg vials, and has a reconstituted concentration of 1000 µg/mL. rFVIIa is also approved for use in many countries for patients with FVII deficiency, although smaller doses are required to achieve hemostasis. In Europe, it is also approved for use in Glanzmann's thrombasthenia.²⁵

The only study to date comparing standard doses of rFVIIa with aPCC was published in 2007.²⁶ The FEIBA versus Novo-seven Comparative (FENOC) study was an open-label, cross-over equivalence study in which patients with hemophilia and inhibitors received standard doses of rFVIIa or aPCC to treat joint bleeding. Because of the statistical parameters used in the design, this study could not declare the two products equivalent, nor could it demonstrate the superiority of either agent.²⁶ However, an important outcome of the study was the high rate of discordant responses in individual patients who had a superior response to one product versus another. This suggests that differences in patient variables may lead to differences in response to bypassing agents.

Alternative dosing regimens for rFVIIa

Continuous infusion

The short half-life of rFVIIa and inconvenience of frequent bolus infusions of rFVIIa has led some investigators to explore continuous infusion of rFVIIa.^{27–31} Continuous infusion of FVIII or FIX is an established practice to control bleeding in hemophilic patients, especially during major bleeding events or surgery.²⁸ The potential advantages of

continuous infusion are the avoidance of trough levels of factor replacement products and a reduced amount of coagulation factor replacement usage, leading to a reduced financial cost.

The first report of a continuous infusion of rFVIIa was in a 62-year-old male with severe hemophilia A and high titer inhibitory antibodies.²⁷ Due to ongoing bleeding following the surgical repair of an inguinal hernia, he was switched from frequent bolus infusions to a continuous infusion of rFVIIa. Despite this, bleeding continued and he was eventually rescued with porcine FVIII. No relevant preclinical or pharmacokinetic studies were described for this patient. Schulman et al were the first investigators to describe the successful use of a continuous infusion of rFVIIa in 1996.²⁸ Preclinical studies were undertaken to confirm the stability and sterility of rFVIIa in mini-infusion pump systems. When reconstituted under laminar air flow, rFVIIa was shown to be stable and sterile for at least 3 days. The addition of heparin to the reconstituted rFVIIa resulted in a 50% reduction in rFVIIa activity within four hours of the addition of heparin. Bonde and Bech-Jensen also found reduced activity of rFVIIa after mixing with heparin. However, the stability of reconstituted rFVIIa was restored if the pH of the heparin solution was adjusted to 7.0 prior to mixing with rFVIIa.³¹ Prior to infusing rFVIIa in patients, Schulman et al then determined the pharmacokinetics of rFVIIa in individual patients.²⁸ Based on the clearance, patients were infused with a rFVIIa bolus dose of 90 µg/kg and given a continuous infusion of rFVIIa, aimed at keeping their clotting factor VII activity (FVII:C) level at 10 U/mL. Two patients received rFVIIa as a continuous infusion during 2 surgical procedures each. Hemostasis was achieved for each procedure. One of the patients developed thrombophlebitis during his first surgical procedure. During his next procedure, low molecular weight heparin was added to the reconstituted rFVIIa, with resolution of his thrombophlebitis. The amount of rFVIIa used for these procedures was estimated to be 50% of that which would have been used had the patients received bolus infusions.

Since then, over 25 studies of continuous infusion of rFVIIa have been reported.^{32–37} The majority of reports are open-label, nonblinded, uncontrolled case studies or small series. Bolus doses range from 75 to 180 µg/kg, and target FVII:C levels were 10–30 U/mL. The continuous infusion ranged from 4.7 to 50 µg/kg/hour. Overall, continuous infusion was reported to be successful in over 80% of cases.³² This result should be interpreted with caution due to the potential for publication bias, in that case studies and small series are more likely to be published if they show a positive result.

A review of cases from the Netherlands suggested that continuous infusions of rFVIIa may be ineffective for oral cavity bleeding.³³ Some investigators have suggested that higher doses of rFVIIa may be needed to achieve the burst of thrombin necessary to achieve hemostasis and have aimed for FVII:C levels of greater than 10 U/mL.^{32,34} However, one study which compared higher-dose continuous infusion (30 µg/kg/hour) to lower dosing could not demonstrate an improved overall hemostatic benefit.³⁵ Another study obtained equal efficacy of hemostasis when comparing high-dose continuous infusion (50 µg/kg/hour) to bolus infusions of 90 µg/kg every two hours.³⁶ However, the factor utilization in the continuous infusion arm of this study was higher than in the bolus group. A third group used high-dose continuous infusion (50 µg/kg/hour), based on previous experience with treatment failures using standard continuous infusion dosing.³⁷ Although the authors claimed “reasonable hemostasis”, a review of their data revealed that only five of their nine patients achieved and maintained hemostasis during surgery and for the first 24 hours postoperatively. Only three of the nine were able to maintain hemostasis for the entire duration of continuous infusion.³⁷ It should be pointed out that using continuous infusion of doses of >45 µg/kg/hour eliminates any economic advantage over bolus infusions of 90 µg/kg given every two hours.

Continuous infusion of rFVIIa has been complicated by nontrivial thrombophlebitis. This has been alleviated by parallel infusions of heparin or saline.

High-dose recombinant activated factor VII

Several studies have confirmed that a burst in thrombin activity is critical for the achievement of normal hemostasis.^{8,9,15,38} Doses of rFVIIa 90 µg/kg can achieve plasma FVIIa concentrations of 50 nM, and approach the normal burst of thrombin during *in vitro* fibrin clot formation. FVIIa 150 nM appears to be necessary to achieve normalization of the thrombin burst.^{38,39} This suggests that higher doses of rFVIIa may be necessary to achieve normal thrombin activity in patients with hemophilia and inhibitors. Initial anecdotal data suggested that this is indeed the case, with several reports of improved hemostasis using doses of rFVIIa up to 300 µg/kg.^{35,40} The high doses were well tolerated without thrombotic events reported. Based on the *in vitro* data and the anecdotal reports, several studies were initiated to examine the use of high dose rFVIIa in hemophilic patients with inhibitors.

In 2005, the Hemophilia and Thrombosis Research Society published the results of a review of its database on rFVIIa

use.³⁹ Thirty-eight congenital hemophilic patients with inhibitors were reviewed for this study. These patients had 555 bleeding episodes treated with rFVIIa. Bleeding stopped in 97% of patients receiving doses of rFVIIa >200 µg/kg versus 84% in patients receiving doses <200 µg/kg. This difference was statistically significant. Doses up to 346 µg/kg were given without any thrombotic events reported.

A prospective trial of rFVIIa use in the home setting to treat hemophiliacs with inhibitors was published by Santagostino in 2005.⁴¹ Patients were randomized in an open-label, cross-over study to receive either 90 µg/kg, repeated as necessary every three hours, or a single high dose of 270 µg/kg. Response was determined using a visual analog scale and was equivalent between the two treatment arms over 48 hours of assessment. The amount of rFVIIa used did not differ between the two groups, nor did the adverse event profile. This study demonstrated that a single high dose of rFVIIa could be given with efficacy equal to that of repeated standard doses, with much greater convenience and similar economic costs.

In another multicenter, randomized, cross-over trial, patients were randomized in a blinded fashion to receive rFVIIa 270 µg/kg followed by two bolus infusions of saline three hours apart or rFVIIa 90 µg/kg given every three hours. This study also demonstrated equal efficacy with either regimen in treating hemarthrosis in the home setting.⁴²

A third randomized, multicenter trial not only compared efficacy between standard- and high-dose rFVIIa, but also with an aPCC.⁴³ Patients were randomized in a blinded fashion to receive high-dose rFVIIa (270 µg/kg) followed by two infusions of saline three hours apart, or standard dose rFVIIa given every three hours for three doses. Patients were also randomized to a standard dose of aPCC (74 U/kg), but not in a blinded fashion due to the appearance and volume of the aPCC infusion. The global assessment showed no significant difference between the treatment arms, but the aPCC arm was statistically more likely to use a rescue medication (36%) than the high-dose rFVIIa (8%). Unlike the FENOC study, this trial compared high-dose rFVIIa with aPCC and suggested an improved response. There were no significant adverse events noted with any of the treatment arms.

These studies suggest that high doses of rFVIIa can be used with equal efficacy and safety to standard dose rFVIIa, but with improved convenience. However, all of the studies were hampered by small sample size, with a maximum of just over 20 patients in each treatment arm.^{39,41–43} Given the rarity of hemophilic patients with inhibitors, it is doubtful that larger studies with improved power to detect statistical differences between treatments will be undertaken. In

2007, the European Medicines Agency approved the use of single high-dose rFVIIa to treat mild to moderate bleeds in hemophilic patients with inhibitors.⁴⁴

Prophylaxis

One of the principal complications of hemophilia is the development of arthropathy due to recurrent hemarthrosis. This complication has now been shown to be preventable by prophylactic infusions of FVIII or FIX.¹ Initial studies of prophylaxis used frequent infusions of coagulation factor aimed at keeping trough factor levels greater than 1%. Subsequent studies have shown that less frequent infusions may be successful in preventing hemarthrosis, suggesting that the biologic effect of replacement therapy may be significantly longer than any effect measured by laboratory tests.⁴⁵

Because the half-life of rFVIIa is only two hours, one would not intuitively expect this agent to be effective in preventing arthritic complications in people with hemophilia and inhibitors. Owing to the potential for an extended biologic effect of rFVIIa compared with laboratory measurement, some investigators have been prompted to use rFVIIa prophylactically.^{20,46–49} As with all other uses of rFVIIa, initial investigations involved case reports or small series. These studies demonstrated a reduction in the number of bleeding episodes while patients received prophylactic administration of rFVIIa compared with the months preceding its use.

A prospective randomized trial of either 90 µg/kg/day or 270 µg/kg/day of rFVIIa was done in 38 hemophilic patients with inhibitors.⁵⁰ Bleeding episodes were determined for the three months preceding prophylaxis, during three months of prophylaxis, and for three months following prophylaxis. The number of bleeding episodes during prophylaxis was reduced by 45% and 59% with rFVIIa 90 µg/kg and 270 µg/kg, respectively. There was not a statistically significant difference in bleeding reduction between the two groups. Health-related quality of life and quality-adjusted life years were also improved by prophylaxis.⁵¹ However, the economic burden of prophylaxis with rFVIIa is substantial, with annual rFVIIa costs potentially exceeding one million dollars per year.⁴⁶

Safety

Because of the ability of rFVIIa to generate a fibrin clot at sites of tissue factor exposure, there is concern that infusions of rFVIIa may lead to thromboembolic events. Indeed, reviews of the MedWatch Pharmacovigilance of the US Food and Drug Agency (FDA) and the FDA Adverse Events Reporting System suggested a relatively high rate of thromboembolic events associated with rFVIIa use.^{52,53} However, these reports included both

on- and off-label uses. Abshire and Kenet reviewed the prevalence of thromboembolic events in patients with congenital or acquired hemophilia and inhibitors who received rFVIIa. Their initial review covered the years 1996–2003.⁵⁴ Because use of high doses of rFVIIa became more prevalent after 2003, they presented an updated review in 2008.⁵⁵ Overall, over 1.5 million doses of rFVIIa were given, with 55 thromboembolic events reported. This prevalence of thromboembolic events of just under 4/100,000 doses did not seem to differ between the two time periods reviewed. Based on these data, it appears that rFVIIa is quite safe for use in hemophilic patients with inhibitors, and the risk of thromboembolic events does not appear to be increased by high-dose infusions. Off-label use may be associated with thromboembolic risk.

Off-label uses of rFVIIa

Although not initially approved for use in FVII deficiency, accumulated anecdotal use led to the approval of rFVIIa in many parts of the world for treating bleeding episodes in patients with FVII deficiency.²⁵ However, because rFVIIa is competing with a lower concentration of FVII for tissue factor in patients with FVII deficiency, lower doses are used. Similar approval has been granted for qualitative platelet disorders, specifically Glanzmann's thrombasthenia.²⁵ Following initial reports of success using rFVIIa in platelet disorders and FVII deficiency, rFVIIa was soon found to be useful in several clinical bleeding situations including trauma, surgical bleeding, obstetric bleeding, intracranial hemorrhage, liver disease, hematopoietic stem cell transplant, von Willebrand disease, and neonatal bleeding.^{56,57} A review of all of the off-label uses of rFVIIa is beyond the scope of this paper, and the reader is referred to several reviews.^{58–60} One recent meta-analysis of controlled trials of rFVIIa in nonhemophilic bleeding revealed that rFVIIa can reduce the number of red cell transfusions, and showed a trend toward reducing mortality.⁶¹ Overall, the number of thromboembolic events were not increased compared with control groups, but the number of arterial thrombotic events was statistically higher (4.5% versus 2%, respectively).

Modified activated factor VII

Because the short half-life of rFVIIa requires frequent dosing, several investigators are pursuing activated FVII molecules with improved pharmacokinetic and pharmacodynamic properties.^{62–64} This could provide several advantages, including a reduced need for intravenous injections, longer protection against bleeding episodes, and a reduced amount of rFVIIa used. Several strategies have been adopted, including

a modification of the amino acid sequence of FVII, stabilization of the molecule with liposomes or pegylation, or fusion proteins with albumin. Investigations into modified rFVIIa are in early clinical and preclinical development.

Summary

rFVIIa is a safe alternative to PCCs or aPCCs in the treatment of patients with congenital or acquired hemophilia and inhibitors. Using standard doses, it seems to be as effective as aPCCs in controlling acute bleeding, and a high dose of rFVIIa may be more effective. The principal limitation of this agent is the inconvenience of frequent infusions and the economic costs. Using high doses of rFVIIa can ameliorate some of the difficulties with frequent dosing. Continuous infusions of rFVIIa may alleviate some of the economic costs, although the economic benefit is eliminated by using higher doses of continuous infusions. Since controversy remains as to the appropriate dose of continuously infused rFVIIa, this method of infusion at present should be reserved for clinical studies. Using rFVIIa prophylactically to prevent bleeding episodes is intriguing, especially given its short circulating half-life. However, until additional data are available, especially regarding optimal prophylactic doses and intervals, the prophylactic use of rFVIIa should also be reserved for clinical studies, especially when one considers the economic costs of rFVIIa.

Disclosure

The author reports no conflict of interest in this work.

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