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REVIEW ARTICLE

Recombinant factor VIIa: review of efficacy, dosing regimens and safety in patients with congenital and acquired factor VIII or IX inhibitors

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Summary. Recombinant factor (rF)VIIa has been available to clinicians since 1996 and has an excellent safety record after almost three-quarters of a million doses have been administered. This paper will review the current clinical experience with rFVIIa dosing in acquired and congenital hemophilia with inhibitors and chronicle all spontaneous and clinical trial reports of thrombotic adverse events as of April 2003. Standard dosing of rFVIIa (90 μg kg^{-1}) allows binding of FVIIa to the surface of an activated platelet and can directly activate factor X in the absence of tissue factor. Experience with bolus dosing suggests that higher dosing (> 200 μg kg^{-1}) may be more efficacious in treating hemophilia patients. Clinical trials are ongoing to validate this observation. Continuous infusion dosing may be efficacious for major surgery but high infusion rates (50 μg kg^{-1} h^{-1}) might be needed. The relationship between dose of rFVIIa, amount of thrombin generated and measurable FVIIa level is still not known and perhaps newer testing which measures thrombin generation might be more advantageous. Relatively few thrombotic events have been associated with rFVIIa. Known factors predisposing to thrombosis were present in 20 of the 25 (80%) hemophilia patients who were reported spontaneously or who developed a thrombosis during a clinical trial. Additionally, thrombotic events have not increased despite a growing experience with higher dosing of rFVIIa.

Keywords: FIX inhibitor, FVIII inhibitors, recombinant FVIIa.

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Introduction

Recombinant factor (rF)VIIa was first approved in Europe in 1996 for the treatment of bleeding episodes in patients with congenital hemophilia and inhibitors to FVIII or FIX or acquired hemophilia. From this period until April 2003, more than 700 000 standard doses (90 μg kg^{-1} for a 40-kg individual) of rFVIIa have been administered for congenital and acquired hemophilia (data on file, Novo Nordisk A/S, Virum, Denmark). Despite substantial use of rFVIIa, relatively few adverse events have occurred, strongly supporting the safety of the product.

This review will briefly describe the mechanism of action of rFVIIa, its role in accentuating thrombin generation where FVIII and FIX are reduced or absent, and how these translate into therapeutic efficacy for control of bleeding. The current clinical experience with different dosing regimens of rFVIIa will be reviewed in both the hemophilia home treatment and surgical settings, with a focus upon the safety profile in patients with hemophilia and inhibitors. All spontaneous reports of thrombotic events in patients with congenital or acquired hemophilia with inhibitors reported as of April 2003 will be reviewed.

Mechanism of action

FVIIa is an important contributor to the initiation of hemostasis. After vascular injury, FVIIa binds to its receptor tissue factor (TF) on the surfaces of TF-bearing cells. The TF–FVIIa complex, in association with factor (F)Va, generates small amounts of factor (F)Xa and thrombin (Fig. 1). Thrombin activates platelets recruited to the site of vascular injury, with resultant exposure of phosphatidylserine [1,2]. These activated platelets then serve as a template for the binding of FIXa, FVIIIa, FXa and FVa, resulting in the formation of the prothrombinase complex of FVa and FXa on the surface of activated platelets. As a result, larger amounts of thrombin are then generated, also referred to as the 'thrombin burst' [3]. As more thrombin is generated, positive feedback

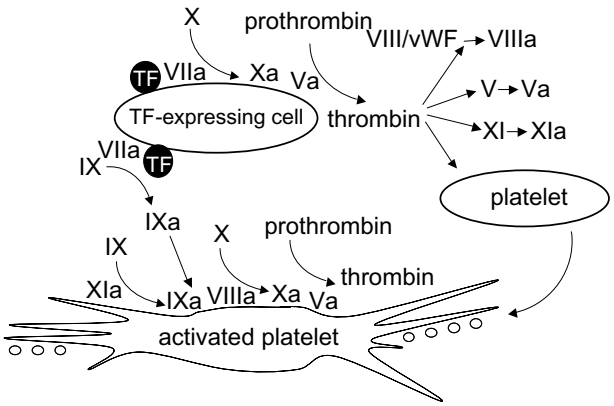

Fig. 1. Model of normal hemostasis depicting essential role of tissue factor (TF)/factor (F)VIIa in initiating thrombin generation and subsequent key interaction of factors XI, IX, VIII on the surface of the platelet with resultant larger thrombin burst.

loops with FV, FVIII, and factor (F)XI occur. Cross-linked fibrin is formed by thrombin activation of factor (F)XIII to FXIIIa, producing a more stable, covalently linked clot, protected from degradation by the thrombin-activatable fibrinolysis inhibitor (TAFI).

In pharmacological concentrations (26–50 nM), rFVIIa can bind to the surface of activated platelets and directly activate FX in the absence of TF [2]. The platelet surface FXa can then, in complex with FVa, lead to a thrombin burst in the absence of FVIII or FIX. The mechanism by which clot formation is kept in balance involves inhibitors of the TF–FVIIa complex, most notably, tissue factor pathway inhibitor (TFPI), which rapidly inhibits the TF–FVIIa complex in the vascular space. Antithrombin III (ATIII), in the presence of heparin, may also inactivate the TF–FVIIa complex on the platelet surface [4]. Both TF and phospholipids remain at the site of injury where inhibitors to the TF–rFVIIa complex are active [5], thereby minimizing systemic activation of the clotting system.

The variability, rate, and quantity of thrombin production *in vivo* may affect clot formation and stability. Interpatient variability in thrombin generation has been described [6]. Higher doses of rFVIIa generate a more rapid thrombin burst, which has been shown to produce a more stable fibrin clot, less prone to fibrinolysis [7,8]. The inhibition of fibrinolysis may in part be due to activation of the TAFI via thrombin [9]. This fibrin clot then functions as a more tightly woven, dense supporting structure on which to lay additional fibrin in support of wound healing. In a cell-based model of thrombin generation in the absence of FIX or FXI, addition of 50 nm rFVIIa significantly increased, but did not normalize, thrombin generation [2].

Pharmacokinetics

rFVIIa has a volume of distribution two to three times that of plasma, but the volume of distribution at steady state is slightly smaller in normal volunteers compared with patients with hemophilia. Other pharmacokinetic parameters are similar among several adult populations, including patients with hemophilia, those with cirrhosis, and healthy volunteers pretreated with acenocoumarol [10]. The median clearance in adult patients with hemophilia is approximately 32 mL kg^{-1} h^{-1} and the mean half-life is 2.72 h [11]. Clearance and half-life are dose-independent. Pharmacokinetic values appear to be similar in both bleeding and non-bleeding patients. Interpatient variability in clearance (approximately 10-fold) and half-life occur, which plays an important role in determining the infusion rate necessary to provide a desired steady-state concentration when administering rFVIIa by continuous infusion [12,13]. Pediatric hemophilia patients have different pharmacokinetic parameters, with a shorter half-life compared with adults (1.32 h vs. 2.72 h), leading to increased clearance [14]. This potentially could be important when considering dose optimization in children, as dosing greater than the currently recommended 90 μg kg^{-1} per dose may be necessary to arrest bleeding.

Dosing

Background

The first reported use of rFVIIa occurred in 1988 in an individual with hemophilia and a high-titer inhibitor undergoing open synovectomy. Fibrin glue and tranexamic acid were also utilized and the procedure was successful without excessive bleeding [15]. Following this case, the use of rFVIIa in a number of elective surgical procedures, as well as in various bleeding episodes in patients with acquired and congenital hemophilia and inhibitors, has been reported [16–21]. rFVIIa is currently considered a safe and effective treatment for bleeding in patients with inhibitors. While the optimal dose and interval have not yet been determined, evidence is accumulating that initial bolus doses in excess of 200 μg kg^{-1} may result in better hemostatic control [22].

Even though the minimum rFVIIa level that is necessary to maintain hemostasis is not known, some pharmacokinetic studies and early clinical work suggest that rFVIIa doses of 17.5 μg kg^{-1} (which produces a trough level of 5 U mL^{-1}) may not be adequate to control bleeding in the inhibitor population [11]. Indeed, trough rFVIIa levels of at least 6–8 U mL^{-1} attained 2 h after a bolus dose may be required to achieve adequate hemostasis in this population. Some data indicate that levels > 10–15 U mL^{-1} FVII:C might be necessary [23]. A trough level of 10 U mL^{-1} and a peak level of 50 U mL^{-1} are provided with the standard 90 μg kg^{-1} dose of rFVIIa [20]. Other studies suggest that a slightly greater bolus dose of 100 μg kg^{-1} will achieve higher peak FVII:C levels of 70–90 U mL^{-1} [24].

The short half-life of rFVIIa has supported dosing recommendations for more frequent bolus injections. Dosing schedules beginning with a bolus of 90–120 μg kg^{-1}, given initially every second hour and followed by similar dosing at increasing intervals, have been effective for both treatment of acute bleeding episodes and prevention of bleeding associated with elective surgery [25]. We will review those studies which have investigated bolus and continuous infusion of rFVIIa in the

hospital, home, and surgical settings. Efficacy parameters within these studies have been variably defined. Usually, effective hemostasis is described as complete or substantial decrease in hemorrhage and/or definite relief of pain, swelling or immobility, whereas partially effective hemostasis requires some decrease in bleeding or improvement in pain, swelling or mobility. Treatment is considered ineffective if no improvement in hemorrhage or bleeding symptoms occurs.

Bolus dosing: hospital setting

Lusher and colleagues compared the efficacy of two dosing regimens of rFVIIa in a randomized fashion among hemophilia patients with or without inhibitors with acute bleeding episodes [26]. All patients traveled to a treatment center to receive 35 or 70 μg kg^{-1} rFVIIa every 2.5 h for up to six doses. One hundred and seventy-nine bleeding episodes (81% hemarthroses) were treated. There was no significant difference in efficacy (71%) between either dose group for the treatment of acute joint or muscle bleeds, nor in the mean number of rFVIIa doses required (2.7 and 3.1 for the 35 μg kg^{-1} and 70 μg kg^{-1} groups, respectively) for bleed resolution. This lack of difference in efficacy may have been the result of delay in initiating treatment (8.4 h and 10 h for the lower and higher dose groups) and because of this delay in treatment, the lowest hemostatic dose could not be discerned from this study.

O'Connell *et al*. retrospectively analyzed the treatment of 12 children undergoing 20 minor surgical procedures at two centers [27]. The dose of rFVIIa used was 90 μg kg^{-1} every 2 h for the first 24 h postoperatively, followed by rFVIIa administration every 3 or 4 h for the next 24–48 h. Concomitant antifibrinolytic agents were utilized. Nineteen of 20 surgical procedures involved insertion or removal of a central venous catheter. The other surgical procedure was multiple dental extractions. Patients were treated for a mean of 48 h with no bleeding complications noted. Minor bleeding occurred in two patients at the catheter insertion site 72 h postoperatively, but was controlled by re-treatment. The same study also reported three patients with acute life- or limb-threatening bleeding [27]. Three mouth bleeds, one port bleed and one forearm bleed with neurological symptoms were treated using the same dosing schedules as above, with patients receiving a median total dose of 17.1 mg of rFVIIa (range 2.4–46.8 mg). Half of the bleeding episodes resolved with two to three doses. Topical fibrin glue was utilized in one patient with a frenulum tear.

Finally, as part of the compassionate use program prior to licensure, 23 patients with severe hemophilia or acquired inhibitors received rFVIIa at doses of 90 μg kg^{-1} every 2 h for 35 limb-threatening joint or muscle bleeds that were unresponsive to alternative therapies [28]. Hemostasis was effective in 86% and partially effective in 11% of episodes.

Bolus dosing: home setting

Four studies have investigated bolus dosing in the home setting [29–32]. All studies utilized 90 μg kg^{-1} every 2–3 h, primarily for treating joint bleeding. Assessment of efficacy was performed by the patient or caregiver. Hemostasis was effective in 86–92% of patients after a mean of two doses [29,30]. Ingerslev *et al*. treated 50 bleeding episodes, mostly early joint bleeds ($n = 30$) or muscle hematomas ($n = 8$) in five hemophilia A patients with inhibitors. A mean of 2.02 doses of rFVIIa provided adequate hemostasis and 86% of patients stopped bleeding with two doses [29]. The US home treatment study was established to assess the efficacy and safety of rFVIIa for the treatment of mild to moderate bleeds in inhibitor patients. Sixty hemophilia A and B patients with inhibitors were enrolled and 877 bleeds treated in 56 evaluable patients on an intention-to-treat basis. On average, mild or moderate bleeds were treated with one to three injections of rVIIa (90 μg kg^{-1}) at 3-h intervals. The primary efficacy variables for the Home Treatment Study were hemostasis within three injections of rFVIIa and maintenance of hemostasis for at least 24 h. In the intent-to-treat analysis, rFVIIa was effective in achieving hemostasis in 775/877 (88%) bleeds, with hemostasis maintained for 24 h in 720/775 (93%) of bleeds. For evaluable bleeds (614 bleeds in 52 patients met the protocol criteria), hemostasis was achieved in 92% of cases. For all treatment outcomes, an effective response was reported for muscle (91%), target joint (86%), and non-target joint bleeds (88%). The mean time from onset of bleed to first treatment was 1.2 h, and 92% achieved an excellent or effective response with a median of 2.2 doses of rFVIIa [30]. In the 16 cases described by Laurian *et al*. 158 bleeds were treated with 90 μg kg^{-1} rFVIIa, with 74% achieving hemostasis, requiring a mean of 3.8 treatments [31]. Treatment was usually initiated 1–3 h after first noticing the bleed.

All studies showed a significant association between early treatment, response rate and number of doses utilized. Santagostino *et al*. evaluated a total of 53 bleeding episodes in patients with high-responding inhibitors, or with high-titer acquired anti-FVIII antibodies [32]. A median of two doses of rFVIIa (range one to four) were given per bleeding episode, and the drug was found effective in 42 episodes (79%), partially effective in six (11%) and ineffective in five (10%). Effective treatments started earlier; the median time from the onset of bleeding to therapy was 0.6 h for effective therapy vs. 2.7 h ($P = 0.02$) for partially or ineffective rFVIIa treatment. Earlier onset of treatment was also significantly associated with less rFVIIa utilized (median 1.5 doses vs. 3; $P = 0.007$).

Efficacy data from the compassionate use studies (very long delay in initiating rFVIIa treatment) compared with dose-finding (some delay) and home therapy studies (treatment generally very soon after the onset of bleeding) suggest that early administration of rFVIIa is more effective [33]. In the compassionate use studies, the mean time from onset of the bleed until first rFVIIa administration was 2.5 days (range 0.3–20.7 days). The dose of rFVIIa utilized was 60 to120 μg kg^{-1}. Only 61% of patients achieved an excellent or effective response, and the mean number of doses required to control bleeding was 22.

Bolus dosing: surgical setting

Lusher has reviewed the experience with rFVIIa in 103 patients undergoing major surgery utilizing a conventional dosing interval (every 2–3 h), with 81% of patients obtaining a good hemostatic response [18]. In contrast, in a report by Gringeri and colleagues, a slightly lower bolus dose of 75 μg kg^{-1} utilizing a conventional dosing interval (every 2–3 h for 2 days) did not prevent re-bleeding in a patient undergoing inguinal hernioplasty [34]. The lower bolus dosing schedule in this patient may have played a role in the decreased efficacy. Accordingly, a dose-finding study was crucial to answer the question of proper dosing in the surgical setting.

Shapiro *et al.* compared two dosing schedules in a prospective randomized blinded study conducted among 28 hemophilia patients with inhibitors and one acquired hemophilia patient, all undergoing either major or minor surgery [35]. Intravenous rFVIIa doses of 35 vs. 90 μg kg^{-1} were administered pre-, peri- and postoperatively every 2 h for 48 h. Blinded dosing was continued every 2–6 h for an additional 3 days. After a maximum of 5 days, the patient could be administered rFVIIa in non-blinded fashion at 90 μg kg^{-1} until the end of the treatment period. For the 90 μg kg^{-1} dosing arm, 83% of patients undergoing major surgery had satisfactory hemostasis postoperatively through day 5. In contrast, though hemostasis was determined to be effective during surgery for the lower dosing arm, efficacy at the 35 μg kg^{-1} arm dropped from 80% at day 1 to 40% at day 5, suggesting that this dose was suboptimal for major surgical procedures. This study did not allow the use of antifibrinolytics or fibrin glue, two agents utilized more frequently within the European community [19].

Continuous infusion

The inconvenience of frequent bolus injections and the potential risk of bleeding complications seen with trough levels of FVIIa (especially when prolonged treatment is necessary for surgical patients) or the possibility of missed or delayed doses have prompted consideration of the use of continuous infusion of rFVIIa in some hemophilia treatment centers. Continuous infusion of rFVIIa can be easily administered via minipumps [12,36,37]. Despite theoretical advantages, administration of rFVIIa by continuous infusion is not a currently approved delivery method and data regarding its efficacy are controversial. Also, because of the effect of the thrombin 'burst' upon fibrin clot generation and its susceptibility to lysis [7], recurrent bolus dosing of rFVIIa may provide a better hemostatic effect than continuous infusion. If continous infusion is utilized via a peripheral vein, potential thrombophlebitis can be minimized by adding normal saline. Use of heparin should be avoided as it can lower FVII:C levels [37]. Continuous infusion may be associated with laboratory markers of thrombin activation but does not appear to increase the risk of systemic thrombosis [36].

Administration of an initial bolus dose of 90 μg kg^{-1}, followed by continuous infusion according to the patient's individual pharmacokinetics, can maintain plasma FVII:C levels above a predetermined trough (10 U mL^{-1}), although higher FVII:C levels may be needed in major orthopedic surgery [38]. Following the first report by Schulman *et al.* in which two hemophilia patients with inhibitors underwent a total of three orthopedic procedures and a wound revision [37], the use of continuous infusion rFVIIa has expanded to the treatment of a variety of surgical procedures [40–43], summarized in a review by Shapiro [25].

A commonly utilized continuous infusion regimen includes an initial bolus dose of 90–120 μg kg^{-1} followed by continuous rFVIIa administration at an initial rate of 14–16.5 μg kg^{-1} h^{-1}, thereafter adjusting rates to the individual patient's clearance rate, in order to maintain FVII:C levels above the presumed hemostatic trough of 10 U mL^{-1}. This dosing regimen was effective in a small surgical population studied [44,45], but less effective (65–70%) when utilized for acute bleeding and hemarthrosis. Schulman reported on the use of continuous-infusion rFVIIa in 20 bleeding events (26 interventions), in which the targeted FVII:C level was approximately 10 U mL^{-1} [12,46]. The treatment was efficacious in 91% of patients and was significantly more effective if antifibrinolytics were used (4% vs. 33% hemorrhages, $P = 0.033$). However, in the study of Smith *et al.*, effective hemostasis was achieved in only one of two minor procedures and two of six major surgeries using a similar dosing regimen [47]. Antifibrinolytic use was not allowed in this study and efficacy did not correlate with the FVII:C levels obtained. Further investigation into the continuous-infusion dosing schedule needed for major orthopedic surgery suggests that an infusion rate of 50 μg kg h^{-1} (plasma FVII:C levels > 30 U mL^{-1}) may be needed [38]. The ranges of other reported dosing regimens have included initial boluses of 75–150 μg kg^{-1} with continuous infusion rates of 4.7–50 μg kg^{-1} h^{-1}, target FVII:C of 10–30 U mL^{-1}, and actual FVII:C values of 5.2–59 U mL^{-1} [48]. Administration of rFVIIa by continuous infusion has been found to be effective in 82% of 77 cases, partially effective in 6% and ineffective in 12% [48].

From a cost standpoint, utilizing standard dosing continuous infusion schedules, the average daily rFVIIa consumption could theoretically be 450 μg kg^{-1} for the first day, followed by a total daily amount of 360 μg kg^{-1} or less depending upon the individual clearance adjustment. In contrast, patients treated with bolus injections might require up to 1080 μg kg^{-1} of rFVIIa for the first 2 days of treatment, followed by 360–540 μg kg^{-1} day^{-1} thereafter. However, if repeated bolus doses are used in conjunction with continuous infusion, the utilization of rFVIIa may be higher than with some bolus dosing regimens, and as previously suggested by the Dutch group, use of continuous infusion in oral cavity bleeds may not be as efficacious. Additionally, as Ludlam and colleagues have reported, higher continuous infusion dosing may be needed for major surgical procedures [38]. Experience with continuous infusion in Australia and Thailand has demonstrated cost savings of up to 25% during the first 12 h of continuous-infusion treatment compared with bolus dosing [49,50]. How-

ever, further dose reduction of 35% in one of these cases was complicated by bleeding, suggesting a lower limit of hemostatic efficacy with this route of administration [49]. The cost of additional boluses for uncontrolled bleeding and treatment for rebleeding also needs to be considered in cost effectiveness studies.

Augmented continuous infusion

Several authors have reported the successful use of higher doses of rFVIIa (160–240 μg kg^{-1}) [51,52]. Accordingly, an augmented regimen utilizing both a higher initial bolus dose and continuous infusion rate (160–180 μg kg^{-1} bolus followed by 30 μg kg^{-1} h^{-1}, respectively) was utilized in an attempt to achieve higher FVII:C steady-state levels (> 20 U mL^{-1}) [45]. This approach was 100% effective in 10 surgical procedures and 72% effective for hemarthrosis and yielded more rapid pain relief and slightly faster bleeding response rates for patients with hemarthroses and muscle bleeds. Santagostino *et al.* treated 25 patients with hemophilia and high-titer inhibitors and three patients with acquired inhibitors with 35 courses of rFVIIa for 10 spontaneous bleeding episodes, 11 major surgical procedures, and 14 minor surgical procedures [53]. Higher bolus doses were given (90–150 μg kg^{-1}, median 100 μg kg^{-1}) and continuous infusion was administered at median rates of 20 μg kg^{-1} h^{-1} for major surgery, and 16–17 μg kg^{-1} h^{-1} for both minor surgery and spontaneous hemorrhage. Tranexamic acid was permitted in this study. Effective hemostasis was obtained in 30 of 35 treatment episodes and FVII:C levels were similar (14–18 U mL^{-1}) in patients regardless of their hemostatic response.

High-dose regimens

In a recent comparison of a continuous-infusion protocol vs. administration of a single-bolus 'mega-dose' rFVIIa (300 μg kg^{-1}) to young patients with hemophilia, higher efficacy and quicker resolution of hemarthroses, along with lower FVIIa consumption, were obtained by the mega-dose schedule compared with the augmented continuous-infusion protocol [45,54]. Two hundred and forty-four bleeding episodes were treated among three patients, with 72% of these episodes occurring in a target joint. One hundred and fourteen of 244 bleeding episodes were treated with the mega-dose schedule and the response rate was 83% (95/114). Most importantly, time to pain relief was short (30 min). Re-bleeding occurred in 10% (11/114 episodes), almost exclusively in the same target joint, but uniformly responded to a second 300 μg kg^{-1} dose.

In a larger study by investigators from the Hemophilia and Thrombosis Research Society, a registry of 556 bleeding episodes (39 patients), mostly on home treatment, were analyzed by dose and efficacy [22]. Bleeding was controlled in 87% of episodes overall but higher dosing (> 200 μg kg^{-1} per dose) was more efficacious compared with lower dosing schedules (< 200 μg kg^{-1} per dose) at a highly significant level (high dose, 97%; low dose, 84%; $P < 0.001$). Importantly, no thrombosis was seen with the higher dosing schedule.

Summary: dosing considerations

At present, the relationship between the dose of rFVIIa, the thrombin burst crucial for stable clot formation, and the actual measurable blood FVII:C levels remains to be clarified. The relative hemostatic benefits of a thrombin burst generated by high peak FVII:C levels achieved by bolus dosing and the potential values of maintaining a sustained FVIIa level by continuous infusion also need further definition. Although evidence is accumulating that higher bolus doses of rFVIIa (> 200 μg kg^{-1}) may be more efficacious for the treatment of acute bleeding, further studies are needed to test this in a prospective manner and to clarify that thrombotic side-effects are, indeed, minimal. Additionally, higher dosing has not been approved by the Food and Drug Administration.

For short courses of therapy, such as for most hemarthroses or muscle bleeds, continuous infusion is impractical. However, continuous infusion might be beneficial for treatment of prolonged bleeding (other than oral bleeding) and for surgical procedures. For uncomplicated bleeding episodes in children, where treatment can be initiated within several hours, a 'mega-dose' of 300 μg kg^{-1} can be considered. Presently, until more safety data can be gathered in adults, the use of rFVIIa 'mega-dose' should only be considered for the treatment of bleeding episodes in young patients. For adults, standard dosing for uncomplicated bleeding episodes (90 μg kg^{-1} every 2–3 h for two to three doses) can be utilized, with gradual lengthening of the dosing interval (to every 4 h for 1–2 days and every 6 h until discontinued). In surgical cases, complicated bleeds or those bleeds in which treatment has been delayed, continuous infusion of rFVIIa can be considered. Optimal dosing for continuous infusion is the focus of current studies. Although daily FVII:C can be drawn and kept above 10 U mL^{-1} with appropriate adjustments in the infusion rate, response has not correlated well with FVII:C levels. Studies are currently underway to determine how best to monitor rFVIIa efficacy in the laboratory. Tests which measure thrombin generation might be the most accurate in this regard. Until these are readily available, however, close monitoring of any clinical bleeding must be maintained, as additional bolus dosing or a higher continuous infusion rate might be needed. The use of antifibrinolytics in conjunction with continuous infusion may increase its efficacy, but has led to concerns about potential thrombotic complications.

Safety

Overview

Relatively few adverse events (AEs) have occurred with the use of rFVIIa within the hemophilia setting, with only a few documented serious AEs possibly or probably related to the product. The focus of this safety overview will be upon those

cases involving clinically significant thrombotic events in patients with congenital or acquired hemophilia with an inhibitor. These cases have been taken from published clinical trial and case reports, or have been spontaneously reported to Novo Nordisk.

To provide perspective on the incidence of thromboembolism with rFVIIa, the background incidence of thrombosis within the general population and within the hemophilia population must be considered. A recent report from France cites the incidence of venous thromboembolism in the general population as 1.83/1000 per year [55]. The annual incidence of venous thromboembolism in the USA is 1.07–1.17/1000, similar to the incidence of cerebrovascular events [56]. The incidence of thrombosis in the hemophilia population is more difficult to discern, but a brief review is instructive. Deep venous thrombosis (DVT) is rare in the absence of indwelling catheters, but has been reported in two patients [57,58]. Catheter-related DVT is more common, seen in 53% of pediatric hemophilia patients (by venogram) in one study [59], and in 63% (10 of 16 patients with severe hemophilia) of patients with a central venous access device determined by various radiographic techniques [60]. Goodnough reported on seven patients with hemophilia A or B who had a myocardial infarction (MI) apparently unrelated to replacement therapy [61]. Additionally, there have been well-documented instances of MI occurring in patients receiving prothrombin complex concentrates or 1-8-deamino-D-arginine vasopressin (DDAVP) [62,63].

Since the licensing of rFVIIa in 1996, more than 700 000 standard doses (90 μg kg^{-1} for a 40-kg individual) of rFVIIa have been administered to patients with congenital hemophilia with inhibitors, or acquired hemophilia. Sixteen thrombotic events {10 arterial [acute myocardial infarction (AMI) or cerebrovascular accident (CVA)] and six venous} and two cases of disseminated intravascular coagulation (DIC) have been spontaneously reported from 1996 through April 2003. Some of these cases have been previously described [64–68].

This review will focus upon these 16 thrombotic events, the clinical details of which can be found in Table 1, and those events associated with a clinical trial (Table 2). Additionally, the five cases of DIC will be reviewed. Many of the cases included in Table 1 are quite complicated and could have had multiple factors contributing to the thrombotic event. Concomitant diagnoses and medications that might have had a bearing on the thrombosis are included. In no case could it be clearly determined that rFVIIa was definitely causally related to the thrombotic event. No new thromboembolic events have been reported during clinical trials with hemophilia patients since August 1999.

Myocardial infarction

AMI has been spontaneously reported in seven patients, three with congenital hemophilia and four with acquired hemophilia (Table 1). Six of these patients were ≥ 70 years old, and most had concomitant risk factors for AMI: advanced age, prior AMI or known coronary artery disease, elevated cholesterol, diabetes mellitus, or hypertension. The one younger patient (age 26) was obese and had concomitant antifibrinolytics and FVIII bypassing activity (FEIBA). The AMI in four patients was not assessed to be related to the use of rFVIIa, one was possibly related, and in two cases the causality could not be determined.

Cerebrovascular events

Three cerebrovascular events [CVA or cerebrovascular thrombosis (CVT)] have been spontaneously reported since 1996 in association with rFVIIa treatment. In these cases, one CVA was possibly attributed to the administration of rFVIIa and the causality in two patients could not be determined. Additionally, there have been three clinical trial-associated CVA/CVT events, and in each case concomitant activated prothrombin complex concentrate (APCC)/FVIII use as well as underlying medical conditions or age may have contributed.

Deep venous thrombosis and pulmonary embolism

DVT and/or pulmonary embolism (PE) has been spontaneously reported in six patients (four with congenital hemophilia and two with acquired hemophilia) receiving rFVIIa. Two events were in the arm, and three were in the lower extremity (one of these lower extremity thromboses was also associated with a PE), and one was reported as an isolated PE. In two cases of thrombosis, a causal relationship with the drug was deemed possible. Details of these cases can be found in Table 1. There was also a report of an internal jugular vein thrombosis after a difficult catheter placement in a 4-year-old child with hemophilia which could possibly have been related to rFVIIa. Interestingly, this patient was receiving low-dose (35 μg kg^{-1}) rFVIIa (Table 2) [35].

Disseminated intravascular coagulation

Five cases in total (clinical trial and spontaneously reported) of DIC associated with the use of rFVIIa have been reported (Tables 1 and 2 and below). Occasionally, some markers of activated coagulation (F1 + 2 fragments) have been noted to be slightly elevated following rFVIIa administration, but without clinical consequence [39]. Activation of coagulation is generally not common with the use of rFVIIa [16,27]; however, caution regarding use in patients with associated disease states where TF is aberrantly expressed is advised. Extravascular release of the TF–FVIIa complex can generate thrombin outside of the vascular system with subsequent fibrinolysis and production of D-dimers and fibrin degradation products (FDPs) [69]. Elevation of some markers of activated coagulation (such as the D-dimer) in isolation is not pathognomonic of DIC.

Of the three cases of DIC in clinical trial patients treated with rFVIIa (Table 2), all occurred with concomitant conditions

Table 1 Thrombotic events spontaneously reported in congenital or acquired hemophilia patients with inhibitors receiving recombinant factor (rF)VIIa during the postmarketing surveillance period (1996 to April 2003)

Adverse event	Age/sex	Diagnosis	Clinical setting	Latency*	Clinical description/predisposing factors
AMI	26/M	Hemophilia A with inhibitor	Soft tissue, muscle bleed	4 h	rFVIIa 84 μg kg^{-1} q 3 h × 2 doses + concomitant antifibrinolytics were given, followed by FEIBA × 2 doses, rFVIIa × 1 dose, then followed by an MI. Obesity (130 kg)
AMI	71/M	Acquired FVIII inhibitor	Cataract surgery	2 h	rFVIIa 78 μg kg^{-1} q 2 h × 2 doses were given. This patient had 2 prior AMIs, a myeloproliferative disorder and Type 2 diabetes
AMI†	72/M	Hemophilia A with inhibitor	Dental extraction	2 h	rFVIIa 102 μg kg^{-1} bolus was given; followed by a CI of 30 μg kg^{-1} h^{-1} with concomitant antifibrinolytics. This patient had prior atherosclerosis and hypertension
AMI	79/M	Hemophilia A with inhibitor	Cataract surgery	5 h	rFVIIa in bolus doses of 103 μg kg^{-1}, then 86 μg kg^{-1} were given q 2 h. This patient had ischemic heart disease, hypertension, and hypercholesterolemia
AMI	77/F	Acquired inhibitor (type unknown)	Ecchymosis, bleeding left buttock	1 day	rFVIIa 85 μg kg^{-1} q 3 h, then 105 μg kg^{-1} q 2 h. This patient had hypertension and a prior MI
AMI	70/F	Acquired FVIII inhibitor	Sublingual hematoma	5 days	rFVIIa 30–50 μg kg^{-1} h^{-1}. CI was started for a sublingual hematoma 3 days after the patient had a cardiac arrest. History of coronary artery disease, CABG 8 months prior to hospitalization. Received tranexamic acid. Patient had the AMI 5 days after the continuous infusion began
AMI†	75/M	Acquired FVIII inhibitor	UGIB following rectal cancer surgery	Not specified	MI occurred 3 days into rFVIIa use; dose was 75 μg kg^{-1} q 3 h. Concomitant tranexamic acid use. This patient had hypertension, hypercholesterolemia (type IIB), septicemia
CVT	91/M	Acquired FVIII inhibitor	Cardiac surgery—severe aortic stenosis	Days; exact no. not specified	rFVIIa 90 μg kg^{-1} bolus then 40 μg kg^{-1} q 6 h × 3 days postop. Normal CT of head while on rFVIIa therapy, but later scans showed 2 cerebral thromboses
CVA	50/F	Acquired FVIII inhibitor	Subdural hematoma	2 days	rFVIIa 90 μg kg^{-1} q 6 h × 2 days. Patient had systemic lupus erythematosis, ESRD, and hypertension. Patient deteriorated on the second day of hospitalization and a head CT showed a questionable cortical infarct
CVT	38/M	Hemophilia A with inhibitor	Suspected intracerebral bleed, knee and GI bleeds	65 days post 1st dose, 22 days post last dose	rFVIIa 80 μg kg^{-1} q 2 h × 3 doses during 9 bleeding episodes, with concomitant tranexamic acid. Patient was discharged after 1 month. One month later, he subsequently developed amnesia, and an MRI showed a right frontal lobe infarct
DVT†	27/M	Hemophilia A with inhibitor	Emergency appendectomy	2 days	rFVIIa 90 μg kg^{-1} q 2 h × 2 days. Suspected DVT near venous access site in right arm
PE	22/M	Hemophilia A with inhibitor	Knee hemarthrosis	2 days	Patient received treatment with APCCs × 2 days, then rFVIIa 90 μg kg^{-1} q 2 h × 2 days, then q 6 h × 2 days, then APCCs × 2 days, rFVIIa for another 2 days, and back to APCCs when event occurred
DVT	39/M	Hemophilia A with inhibitor	Surgery for infected anal fistula	7 days	rFVIIa 90 μg kg^{-1} × 1–2 doses. Right leg DVT
DVT/PE†	57/F	Acquired FVIII inhibitor	Bleeding during cholecystectomy/abscess	2 days	rFVIIa 20–48 μg kg^{-1} × 5 days. This was an obese patient (93 kg); had received porcine FVIII and FEIBA × the prior 13 days. R leg DVT (thrombosis localized around femoral catheter); plus pulmonary embolism with a fatal outcome
DVT	16/M	Hemophilia A with inhibitor	Hematuria	1 month	rFVIIa 90, 120, 200 μg kg^{-1} single doses + FVIII replacement was given. A leg DVT developed; this patient was obese (150 kg) with a sedentary lifestyle

Table 1 (continued)

Adverse event	Age/sex	Diagnosis	Clinical setting	Latency*	Clinical description/predisposing factors
DVT	? age/F	Acquired FVIII inhibitor	Shoulder bleed	Not specified	rFVIIa dose unknown; R arm DVT
DIC	57/M	Hemophilia A with inhibitor	Septic arthritis	11 days	rFVIIa 30 μg kg^{-1} (dosing interval not provided) given ×34 days Patient had a 72-h period of 'subacute DIC' which resolved while patient continued rFVIIa therapy
DIC	70/M	Acquired FIX inhibitor	Post-hemicolectomy	Not specified	rFVIIa and tranexamic acid were given during surgery. Postoperatively, the patient had persistent intra-abdominal bleeding, hypotension; rFVIIa and FEIBA were administered, but the patient died

*Latency, Time interval from last rFVIIa dose to the thrombotic event. † Previously reported in literature. APCC, Activated prothrombin complex concentrate; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CI, continuous infusion; CT, computed tomography; CVA, cerebrovascular accident; CVT, cerebrovascular thrombosis; DVT, deep vein thrombosis; DIC, disseminated intravascular coagulation; ESRD, end-stage renal disease; FEIBA, factor VIII bypassing activity; MRI, magnetic resonance imaging; PE, pulmonary embolism; UGIB, upper gastrointestinal bleed.

Table 2 Clinical trial reports of thrombotic events in congenital or acquired hemophilia patients with inhibitors receiving recombinant factor (rF)VIIa

Adverse event	Age/sex	Diagnosis	Clinical setting	Latency*	Clinical description/predisposing factors
CVT	8/M	Hemophilia A with inhibitor	Subdural hematoma	40 h	rFVIIa 96 μg kg^{-1} q 3 h was given; patient had received prior porcine/human FVIII, APCC therapy. Developed a left suboccipital infarct.
CVT	55/M	Acquired FVIII inhibitor	Hepatic parenchymal/ subcapsular hemorrhage post gall-bladder surgery	9 h	rFVIIa 80 μg kg^{-1} q 2 h × 10 doses; was initially treated with FEIBA. History of multiinfarct dementia, prior CVA, CHF, hypertension; renal disease. Fatal outcome
CVA	81/M	Acquired FVIII inhibitor	GI bleeding	> 8 days	rFVIIa 87–130 μg kg^{-1} bolus, initially treated with porcine/ human FVIII. Developed bilateral DVT, CVA, PE
DVT†	4/M	Hemophilia A with inhibitor	Port placement	2 days	rFVIIa 35 μg kg^{-1} q 2 h. Signs of internal jugular vein thrombosis after difficult PAC placement
DIC†	21 M	Hemophilia A with inhibitor	Surgery for a large hip abscess	4 days	rFVIIa 98 μg kg^{-1} q 3 h × 4 days. Patient had extensive myonecrosis and necrotizing fasciitis from the knee to pelvis, and had a fatal cardiac arrest. An autopsy revealed microthrombi in the pulmonary vasculature
Necrotic bowel/ possible DIC†	36/M	Hemophilia A with inhibitor	Epidural hematoma	14 days	rFVIIa 90 μg kg^{-1} q 2–3 h. Treated initially with APCC. Initial epidural (C6–T12) hematoma; later developed GI bleed and hypotension, and a necrotic bowel requiring resection. This patient had no documented thromboses
DIC†	56/F	Acquired FVIII inhibitor	Recurrent lower GIB	9 days	rFVIIa dose unknown; patient was treated initially with FEIBA

*Latency, Time interval from last rFVIIa dose to the thrombotic event. † Previously reported in literature. APCC, Activated prothrombin complex concentrate; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CT, computed tomography; CVA, cerebrovascular accident; CVT, cerebrovascular thrombosis; DVT, deep vein thrombosis; DIC, disseminated intravascular coagulation; ESRD, end-stage renal disease; FEIBA, factor VIII bypassing activity; PE, pulmonary embolism; GIB, gastrointestinal bleed.

that might have resulted in activated coagulation, and their details are discussed here. One patient (36 F; Table 2) had a gastrointestinal bleed not responsive to treatment with APCC and received rFVIIa 1 week later. This patient had a concomitant epidural hematoma, hypotension, necrotic bowel and laboratory evidence of liver dysfunction as well as DIC [65]. Another case (21 M; Table 2) with laboratory evidence of DIC after rFVIIa use occurred after surgical resection of a massive, necrotic *Salmonella*-related muscle abscess [70]. Bleeding was responsive to plasma and rFVIIa but the patient succumbed to cardiac arrest. Another patient (56 M; Table 2) with acquired hemophilia and a severe gastrointestinal bleed received numerous red cell transfusions with resultant elevated prothrombin time (PT), activated partial thromboplastin time (APTT) and depressed platelet count and fibrinogen consistent with dilution of clotting factors/platelets or possible DIC [71].

There have been two spontaneous reports of DIC (Table 1). One involved a 57-year-old hemophilia A patient with a FVIII inhibitor and septic arthritis. rFVIIa had been used 11 days prior to the onset of a 72-h period of 'subacute DIC'. The other case involved a 70-year-old male with liver disease, acquired FIX deficiency and posthemicolectomy for a suspicious villous polyp. rFVIIa was administered intraoperatively, and the postoperative course was complicated by intra-abdominal hemorrhage, acidosis and hypotension, and eventual death.

Summary: safety issues

The incidence of thrombotic events with the use of rFVIIa is extremely low. It appears to be lower than the thrombotic risk seen with other clotting factor concentrates with known thrombogenic potential, such as prothrombin complex concentrates and FEIBA® [63,72]. Known predisposing factors for thrombosis were present in 15/18 (83%) of the rFVIIa-treated patients with spontaneously reported events, and in five of the seven (71%) clinical trial patients. Of the 25 patients in Tables 1 and 2, 11 had received concomitant therapy with APCCs and/or antifibrinolytic agents. In comparison, 72 thromboembolic events were reported in hemophilia B patients with the use of prothrombin complex concentrates in a worldwide survey from 1987 to 1990 [63]. Some thrombotic events occurred in young patients without predisposing factors. However, in contrast to FEIBA®, there does not appear to be any increase in thrombotic events related to dosage or dosing frequency.

The low incidence of thrombotic events with rFVIIa is noteworthy, especially since the clinical conditions in which the drug is administered often inherently carry a high thrombotic risk. Since rFVIIa activates FX directly upon the surface of activated platelets, an event localized to the site of bleeding, systemic activation of the clotting system seems unlikely. Nonetheless, caution should be entertained in the use of this agent in elderly patients with underlying cardiovascular and other (e.g. obesity) risk factors, or in states of excessive TF production [73]. Additionally, an evaluation of underlying causes of thrombosis should be considered if a patient sustains a thrombotic event when using rFVIIa.

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