Review

Clinical experiences and current evidence for therapeutic recombinant factor VIIa treatment in nontrauma settings

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Abstract

The hemostatic properties of recombinant activated factor VII (rFVIIa) are established in patients with inherited or acquired hemophilia with inhibitors and in patients with congenital factor VII deficiencies. Emerging clinical evidence suggests that there may be a wider role for rFVIIa in the management of hemorrhage associated with traumatic injury/accident and severe bleeding associated with critical surgery. This article considers recent data from studies in which rFVIIa was used in an attempt to control bleeding in clinical situations as diverse as coagulopathy associated with chronic liver disease, massive perioperative bleeding and bleeding during prostatectomy, organ transplantation and orthopedic surgery, uncontrollable obstetric hemorrhage, and intracerebral hemorrhage. In nontrauma settings involving acute and potentially life threatening bleeding, there may be a place for rFVIIa as adjunctive therapy in the control of hemostasis.

Introduction

Since the first reports of hemostatic responses in trauma patients with uncontrolled hemorrhage [1,2], a growing body of literature has addressed the use of recombinant activated factor VII (rFVIIa – NovoSeven®; Novo Nordisk A/S, Bagsværd, Denmark) in settings outside the therapy of hemophilia patients with high titer inhibitors. Several articles (e.g. Hedner and coworkers [3], Roberts and colleagues [4], and other reviews in this supplement) have described the developmental background of this agent, highlighted its mechanism of action, and reviewed its use in a variety of clinical settings, including qualitative and quantitative thrombocytopenic conditions, liver disease, and acquired surgical and medical bleeding conditions in patients with presumed intact hemostatic mechanisms. This literature, along with what appears to be an acceptable early toxicity profile and a putative mechanism of action that involves increased thrombin generation at sites of vascular injury in concert with activated platelets, has pointed toward consideration of the wider use of rFVIIa as a hemostatic agent. However, as in the setting of acute trauma, significant issues of cost, indications, laboratory monitoring, safety, optimal dose, and use with blood products and other hemostatic agents remain to be established for rFVIIa use in patients without acute trauma who do not have hemophilia. In this report we review these issues for clinical conditions that are likely to be encountered in the operating theatre or intensive care unit.

Hematologic disease (platelet and coagulation factor defects)

Treatment of spontaneous bleeding in patients with hemophilia types A and B who have developed inhibitors to factors VIII and IX, respectively, remains the only indication approved by the Food and Drug Administration for the use of rFVIIa in the USA [5]. In the European Union this treatment is indicated in the setting of surgical bleeds in hemophilia types A and B with inhibitors against factors VIII and IX, respectively; in patients with acquired hemophilia; in patients with congenital factor VII deficiency undergoing surgery or invasive procedures; and in patients with Glanzmann's thrombasthenia. Response rates have been excellent in these patients, in settings ranging from major to home treatment of bleeding episodes. The dose recommended in the package insert (90 μg/kg) is given as an intravenous bolus every 2–3 hours until the bleeding stops. Higher doses are favored by some investigators, and the agent has been safely used in patients receiving concomitant antifibrinolytic agents [6].

Patients with decreased levels of factors VII and XI have successfully been treated with rFVIIa. In factor VII deficient patients doses of 15–20 μg/kg have been given every 2–3 hours, whereas in factor XI deficiency therapeutic doses

DIC = disseminated intravascular coagulation; FFP = fresh frozen plasma; HSCT = hematopoietic stem cell transplantation; ICH = intracerebral hemorrhage; INR = international normalized ratio; OLT = orthotopic liver transplant; PT = prothrombin time; RBC = red blood cell; rFVIIa = recombinant activated factor VII.

of rFVIIa range from 90 to 120 μg/kg, given in a similar schedule [7,8]. As in the hemophilia setting, rFVIIa may also be useful in patients with von Willebrand's disease who have developed antibodies against von Willebrand factor or who fail to respond to conventional therapy [9,10]. Finally, rFVIIa was reported in anecdotal studies to be successful in treating patients with both qualitative and quantitative platelet defects [5]. Because of the complexity involved in diagnosing these disorders, and because of considerations of alternative therapies, treatment of these patients is best undertaken in collaboration with a hematologist specializing in such cases. Based on the mechanism of action, rFVIIa is unlikely to be effective in patients with zero levels of factor X or with severe thrombocytopenia (counts <5000/μl).

The use of rFVIIa in patients with bleeding and complex hematologic disturbances was highlighted in a recent study (reported in abstract form) conducted in patients with severe bleeding complications following hematopoietic stem cell transplantation (HSCT) [11]. In a double blind design comparing placebo and three different doses of rFVIIa (40, 80, and 160 μg/kg), 100 patients with moderate or severe bleeding (lower and upper gastrointestinal tract, hemorrhagic cystitis, pulmonary, intracerebral, and other sites) that occurred 2–180 days after HSCT were treated every 6 hours for 36 hours. Patients who received the intermediate rFVIIa dose of 80 μg/kg were reported to exhibit significant improvements in bleeding status from 0 to 38 hours as compared with standard hemostatic treatment ($P = 0.021$). However, patients who received the other two doses did not improve compared with the placebo patients. Patients were excluded from the study if they had recent thromboembolic events, atherosclerotic disease, disseminated intravascular coagulation (DIC), thrombotic microangiopathy, veno-occlusive disease, or active leukemia (acute mylogenous leukaemia types M3, M4, M5). Further studies are needed to establish optimal and effective dose regimens for rFVIIa in heterogeneous patient populations such as those experiencing bleeding after HSCT.

Liver disease and gastrointestinal bleeding

Orthotopic liver transplantation

Orthotopic liver transplantation (OLT) is commonly associated with excessive blood loss and need for considerable transfusion of blood and blood products. Blood loss may result from surgical causes as well as impaired hemostasis caused by decreased concentrations of coagulation factors, hyperfibrinolysis, and thrombocytopenia. One of the most serious complications of liver transplantation is hepatic artery thrombosis; thus, any measure to improve hemostasis should not increase the risk for thrombosis.

A recent open label, dose finding study conducted by Hendriks and colleagues [12] showed that rFVIIa reduced transfusion requirements in patients undergoing OLT because of chronic end-stage liver disease (Child-Turcotte [Pugh's modification] score B or C). Following an intravenous injection of 80 μg/kg rFVIIa 10 min before the start of surgery, there was a significant reduction in transfusion requirements (both allogenic and autologous) and blood loss between treated patients and control individuals (3.5 l [range 1.4–5.3 l] in treated patients versus 9.8 l [3.7–35 l] in control individuals; $P = 0.004$). However, only six patients were treated with rFVIIa and, of particular concern, the 12 control individuals were previously treated patients whose records were obtained from the hospital database. There were no thrombotic complications. Similar results were observed in a more recent, but again uncontrolled study [13] in which patients received a single bolus dose of rFVIIa (68.37 μg/kg body mass [range 32.88–71.84 μg/kg]) intravenously 10 min before skin incision, without any thrombotic complications.

Two larger scale, double blind studies in patients undergoing OLT also support the efficacy of a single dose of rFVIIa in reducing patient requirements for transfusion products, without any increase in the incidence of thromboembolic complications [14,15]. Planinsic [15] randomly assigned 83 patients, undergoing OLT for end-stage liver disease, to treatment with placebo or a single bolus dose of 20, 40, or 80 μg/kg rFVIIa given 10 min before surgery. In this study, treatment with 80 μg/kg rFVIIa was associated with a significant reduction in requirement for fresh frozen plasma (FFP). A larger study, involving 182 OLT patients, compared the efficacy and safety of doses of 60 μg/kg and 120 μg/kg rFVIIa 10 min before skin incision, followed by repeat dosing every 2 hours until 30 min before the expected start of reperfusion of the transplanted liver [14]. This study assessed the volume of blood products transfused and blood loss during the perisurgical period and for 24 hours after surgery. Within the group of 179 patients who completed the observation period, a significantly higher number of patients receiving rFVIIa avoided red blood cell (RBC) transfusion, with 10% (6/62 patients) avoiding transfusion in the 60 μg/kg group, 7% (4/56) in the 120 μg/kg group, and no avoidances (0/61) in the placebo group ($P < 0.03$).

Partial hepatectomy

The hemostatic efficacy and safety of rFVIIa for the prevention of bleeding episodes in noncirrhotic patients undergoing partial hepatectomy were evaluated in a multicenter, double blind, placebo controlled study involving 204 patients [16]. Patients were randomly assigned to receive either 20 or 80 μg/kg rFVIIa or placebo 5 min before the first skin cut and any clamping procedures, with a second identical dose given 5 hours after first skin cut if time in surgery was anticipated to extend beyond 6 hours. Perioperative RBC transfusion requirements and blood loss were assessed, and safety of therapy was evaluated by means of laboratory monitoring of coagulation parameters and Doppler examination of hepatic vessels and lower extremities for any signs of thromboembolism.

This study found that only 25% of patients treated with 80 μg/kg rFVIIa required transfusion whereas 37% of

placebo patients and 41% of patients receiving 20 μg/kg rFVIIa required transfusion [16]. Although there were no significant differences between the treatment groups in terms of mean erythrocyte requirement in patients receiving erythrocytes (1024 ml for placebo group, 1354 ml for the 20 μg/kg rFVIIa group, and 1036 ml for the 80 μg/kg rFVIIa group) and no differences in intraoperative blood loss, the reduction in hematocrit during surgery was smallest in the 80 μg/kg rFVIIa group, with a significant overall effect of treatment ($P = 0.04$). Thromboembolic events were observed at a similar rate in all three treatment groups. The study investigators concluded that rFVIIa dosing did not reduce, to a statistically significant extent, either the number of patients transfused or the volume of blood products administered.

Liver biopsy

Patients with acute or chronic liver disease may develop a complex coagulopathy including various degrees of thrombocytopenia; a prolonged prothrombin time (PT) due to decreased levels of coagulation factors; and hyperfibrinolysis, which complicates performance of common surgical and medical procedures including dental extraction and liver biopsy [17,18]. Treatment of such patients with FFP or prothrombin complex concentrates may be associated with possible virus transmission, variable effectiveness, and volume overload [19]. Studies conducted in warfarin treated rats and in healthy human volunteers pretreated with anticoagulants [20,21] have suggested that rFVIIa may enhance hemostasis in situations that mimic the coagulation defects seen in chronic severe liver disease.

In a pilot study of patients who did not undergo invasive procedures [22], rFVIIa was given to 10 cirrhotic patients at increasing doses of 5, 20, and 80 μg/kg. The rFVIIa was successively administered at weekly intervals beginning 10 days after initial failure to respond to vitamin K injection. The PT corrected to normal or near normal levels for all doses; more prolonged responses occurred after the higher doses, and there were no episodes of disseminated intravascular coagulation (DIC).

In a blinded, randomized study of rFVIIa dosed at 5, 20, 80, and 120 μg/kg in cirrhotic patients undergoing biopsy [23], a maximum reduction in PT values was observed 30 min after dosing. Furthermore, patients treated with 80 and 120 μg/kg exhibited significantly longer duration of normalization of the PT. Hemostasis, assessed by direct visualization via laparascopic biopsy, was achieved within 10 min in 74% of patients evaluated, but there was no effect attributable to treatment dose. The low volumes of rFVIIa used in these studies and the lack of viral transmission associated with this agent indicate that infectious complications and volume overload should be reduced. Further studies are indicated to determine the risk for thrombosis or DIC.

Gastrointestinal bleeding and cirrhosis

A number of pilot studies suggested that rFVIIa could normalize PTs and might therefore improve hemostasis in patients with cirrhosis and esophageal variceal bleeding associated with abnormal clotting [22,24]. However, the promise of these initial anecdotal reports was not supported in a large recent study [25] in which 245 cirrhotic patients with upper gastrointestinal bleeding were randomly assigned, in a double blind manner, to receive eight doses of placebo versus 100 μg/kg rFVIIa at the start of the study and at 2, 4, 6, 12, 18, 24, and 30 hours thereafter. Blood transfusion was given to maintain the hematocrit between 25% and 30%, and patients were treated according to common guidelines for endoscopy (sclerotherapy and banding) and use of vasoactive treatment (terlipressin, somatostatin, or octreotide). The two study groups were similar in terms of baseline demographic data.

No significant differences were observed in thromboembolic events or mortality, which tended to be slightly smaller in the placebo group than in the treatment group (4/119 versus 7/118 at 5 days and 11/119 versus 16/116 at 42 days) [25]. In a small group of patients with severe esophageal bleeding (variceal bleeders of Child-Turcotte [Pugh's modification] score B or C) there was a marked reduction in bleeding, and control of bleeding was improved. The authors therefore concluded that further studies are warranted to determine which patient groups may benefit from use of rFVIIa.

Reversal of coumadin overdose

Review of the available literature suggests that rFVIIa is efficacious in the reversal of anticoagulant treatment with vitamin K antagonists [26]. Studies have shown that single doses of rFVIIa can normalize international normalized ratio (INR) and PT in healthy volunteers given acenocoumarol treatment at anticoagulant doses. In a group of volunteers pretreated with acenocoumarol, INR was elevated to above 2, factor X and factor IX levels were reduced by 19–46%, protein C levels were reduced by 2–20%, and factor VII levels were reduced by 4–17%. A single dose of 5 μg/kg rFVIIa normalized INR within 12 hours, whereas doses of rFVIIa of above 120 μg/kg were found to correct INR for periods of 24 hours without signs of systemic coagulation.

The ability of rFVIIa to effect rapid reversal of oral anticoagulation in clinical settings has been reported in an uncontrolled case series including patients with an array of comorbid conditions requiring anticoagulant therapy for prevention and management of venous thromboembolism and cardiovascular or cerebrovascular occlusions [27]. In all 13 cases, patients had critically increased INRs requiring immediate reversal of warfarin induced anticoagulation. In five cases the INR was above 10, in four cases patients were deemed to be at risk for clinical hemorrhage, and in four cases the patient required diagnostic or therapeutic interventions involving bleeding risk. The use of rFVIIa at doses

ranging from 15 to 90 μg/kg was associated with rapid and effective correction of prolonged INRs and aversion or reversal of bleeding due to warfarin toxicity; the authors felt that lower doses were as efficacious as the higher doses used in the study. Furthermore because the duration of response to rFVIIa is shorter than the anticoagulant effect of oral agents, patients should be closely followed clinically and carefully monitored after treatment. These patients may also require vitamin K therapy for more long term control of hemostasis.

Surgery and massive transfusion in patients with normal and abnormal preoperative hemostasis

Prostatectomy

Abdominal retropubic prostatectomy is often associated with considerable perioperative blood loss [28]. Friederich and colleagues [29] investigated the prophylactic use of rFVIIa in patients undergoing this operation in a small, double blind study comparing placebo (12 patients) with two different doses rFVIIa (20 μg/kg [eight patients] and 40 μg/kg [16 patients]). The results revealed a dose dependent, significant reduction in perioperative blood loss (1235 ml and 1089 ml in the 20 and 40 μg/kg groups, respectively, versus 2688 ml in the placebo group; $P = 0.001$) and reduced operating room time for treated patients compared with placebo. No patients in the 40 μg/kg group received any transfusions, whereas more than half of the patients in the placebo group required allogenic RBC transfusion. Although the blood loss in the control group appeared to be higher than some centers consider to be the standard, this study remains one of the few randomized, double blind, placebo controlled studies of the use of rFVIIa in patients with normal preoperative hemostasis.

Cardiac surgery

There have been a number of case reports of the use of rFVIIa in patients undergoing various forms of cardiac surgery [30-34]. The use of rFVIIa thus far has usually followed cardiac surgery (valve replacement or bypass grafting) and usually involves the successful use of the agent to help terminate profound postoperative hemorrhage. Although it is intriguing that rFVIIa appears to have been successfully used in a small number of patients without graft thrombosis, to date there have been no placebo controlled studies of the use of rFVIIa in cardiac surgery.

Neurosurgery

There have been two reports of the use of rFVIIa in neurosurgical patients [35,36]. The first [35] reported on the successful use of rFVIIa in a patient with a large recurrent skull base hemaniopericytoma with difficult intraoperative hemostasis. The second report [36] described the use of rFVIIa in nine patients with a variety of different neurosurgical conditions who also had a coagulopathy before surgery. All patients were treated preoperatively with rFVIIa to correct the coagulopathy before surgery. In all cases the use of rFVIIa was successful, and none of the patients developed any procedure related complications.

Orthopedic surgery

In a randomized, controlled, double blind study, Raobaikady and coworkers [37] investigated the prophylactic use of rFVIIa in a group of patients undergoing semielective open reduction on traumatic pelvic and pelvic acetabular fractures. Historically, this group of patients had a mean blood loss of approximately 2.5 l (similar to the blood loss observed in the prostatectomy study conducted by Friederich and colleagues [29]). Patients were randomly assigned to receive 90 μg/kg of either placebo or rFVIIa immediately after skin incision. Based on the results of the study by Friederich and colleagues, it was expected that this would result in at least a 50% reduction in measured blood loss and a reduction in the need for blood transfusion. The measured blood loss in patients receiving rFVIIa was found to be greater than in patients receiving placebo (2070 ml versus 1535 ml). However, when the total blood loss at 48 hours after the start of surgery was also calculated using the method described by Rosencher and coworkers [38], the group receiving rFVIIa had less blood loss (2146 ml versus 2787 ml), although this difference was not statistically significant. It was also noted that a greater number of patients in the placebo group than in the treated group received allogenic blood components (67% versus 46%), but again this difference was not statistically significant. The authors concluded that the prophylactic use of rFVIIa was not justified in fit healthy patients, with normal clotting systems, undergoing major surgery unless there are special circumstances to warrant its use.

Gynecological/obstetric surgery

A case report by Danilos and colleagues [39] described the successful use of rFVIIa (single 80 μg/kg dose) in a patient who underwent a total abdominal hysterectomy with salpingo-oophorectomy and developed postoperative hemorrhage 5 hours after apparently successful initial surgery. Bouwmeester and coworkers [40] described a patient with a massive 42 unit packed RBC transfusion postpartum who responded within 10 min of receiving a single dose of 60 μg/kg rFVIIa.

Other case reports of use of rFVIIa for management of life threatening postpartum hemorrhage include the case of a patient with rapid onset pre-eclampsia requiring delivery via cesarian section who had a deranged coagulation profile, which persisted despite attempts to stem surgical bleeding and correct coagulopathy by transfusion of RBC and blood products [41]. A single dose of rFVIIa 90 μg/kg was found to effect a rapid clinical response, which was evident within 30 min, reducing abdominal drainage within 3 hours such that the patient had no further requirement for RBC transfusion and gradually returned to a normal coagulation profile and platelet count by day 10 after admission.

Ahonen and Jokela [42] recently reported their experience of using rFVIIa in 12 cases of severe postpartum hemorrhage. In 11 cases there was partial or good response to treatment when it was applied after conventional medical and surgical intervention had failed to correct bleeding. These authors suggest that in cases of intractable obstetric bleeding, where there is no other obvious case for hysterectomy, rFVIIa should be considered before resort to radical surgery.

Kidney transplantation

Recombinant activated factor VIIa has been evaluated for its ability to effect hemostasis in a patient admitted to an intensive care unit following his third kidney transplant [43]. The patient had end-stage renal failure caused by mesangiocapillary glomerulonephritis and had been dialysis dependent for 25 years. The postoperative recovery period was complicated by hemodynamic instability and myocardial infarction. Three days after his transplant the patient bled and developed a large perinephric hematoma. He was returned to the operating theatre but no obvious cause for bleeding was found. He was transfused further but was again returned to theatre after more bleeding. He was finally given 70 μg/kg rFVIIa and the bleeding stopped. This use of rFVIIa was despite the patient having recently suffered a myocardial infarction.

Massive transfusion associated with surgery and medical conditions

O'Connell and colleagues [44] described a series of 40 patients who developed massive bleeding that was unresponsive to conventional therapy. These authors reported a series of patients collected from 13 hospitals. The patients described were predominantly patients undergoing surgery, although 10 were medical patients. Only two patients in their series had a history of trauma. The median number of doses of rFVIIa used was two (range 1–18), and the individual doses varied in the range 15–180 μg/kg. Only two patients received more than four doses of rFVIIa. A total of 80% of patients achieved a complete or partial cessation of bleeding after administration of rFVIIa. Eighteen patients stopped bleeding completely and in 14 cases the bleeding slowed significantly. Eight patients (20%) did not achieve hemostasis after administration of rFVIIa. Six of these eight patients had liver disease, and the remaining two had undergone emergency repair of ruptured abdominal aortic aneurysm.

There was no evidence of a dose response, either in patients who achieved hemostasis or in the three cases with thromboembolic complications: hepatic artery thrombosis following transplantation; iliac vein thrombosis following iliac artery and vein manipulation during repair of a postradiotherapy fistula in a patient with bladder cancer; and multiple pulmonary emboli found at autopsy in a patient with disseminated lymphoma, who developed multiorgan system failure following surgery for intractable gastrointestinal bleeding. Of note, antifibrinolytic agents were used in conjunction with rFVIIa in a considerable number of cases, which is consistent with other anecdotal reports of the successful use of tranexamic acid in conjunction with rFVIIa in hemophilia [45].

Intracerebral hemorrhage

Intracerebral hemorrhage (ICH) accounts for between 10% and 30% of strokes and is associated with high mortality and morbidity. It is known that the volume of bleed into the brain is a major predictor of neurological and functional outcome after ICH, and interest in a clinical role for rFVIIa in stroke management has been fueled by recent reports showing that this treatment has a good safety profile in patients with acute ICH and appears to be effective in reducing hemorrhage growth, with resultant improvements in clinical outcome for patients [46,47].

A double blind, placebo controlled study in patients with acute ICH [47] compared the effects of treatment with 40 μg/kg (108 patients), 80 μg/kg (92 patients), or 160 μg/kg (103 patients) of rFVIIa versus placebo (96 patients) on hemorrhage growth, deaths, and functional outcome at 3 months. Treatment was given within 1 hour of a diagnostic computed tomography scan. Compared with a 29% growth in placebo treated patients, ICH volume growths at 24 hours in the 40, 80, and 160 μg/kg rFVIIa treatment groups were 16%, 14%, and 11%, respectively. In terms of reduction in hematoma growth, this reflected 3.3 ml, 4.5 ml, and 5.8 ml reductions, respectively, for the three treatment groups versus placebo. Pooled data for all doses of rFVIIa showed that treatment resulted in a 52% relative reduction in hemorrhage growth compared with placebo ($P = 0.01$). There was a mean increase in hemorrhage volume of 8.7 ml in the placebo group, but the mean increase in patients receiving rFVIIa (all doses combined) was 4.2 ml. Treatment with rFVIIa was associated with a significant increase in numbers of patients with an improved clinical outcome. Three months after ICH it was found that acute rFVIIa treatment effected an absolute reduction in risk for death or severe disability of 16% (death/disability: 69% placebo versus 53% for all doses of rFVIIa combined; $P = 0.004$, all doses versus placebo), and it was shown that treatment with rFVIIa more than doubled a patient's chances of improving one level on the modified Rankin Scale. There was a 38% relative reduction in patient mortality at 3 months (29% for placebo versus 18% for all doses of rFVIIa; $P = 0.02$). However, in this study serious thromboembolic events such as myocardial infarction and cerebral infarction occurred in 7% of rFVIIa-treated patients, as compared with 2% of placebo treated patients ($P < 0.05$) and the exclusion criteria were changed midway through the trial, because of concerns about safety, to exclude patients with a history of thromboembolic disease [47].

Optimal dose, monitoring and concurrent use of blood products

As described in this review, rFVIIa has been used in a range of nontrauma settings and employed at a wide range of

doses for management of hemorrhage that fails to respond to conventional medical and surgical management. The variation in selected doses reflects the history of investigation of this therapy outside the hemophilia setting, in which there was often uncertainty regarding the dose required for optimal hemostatic efficacy, tempered by early concerns that this treatment could have thrombogenic potential.

Given the mechanism of action of rFVIIa, there was concern that activation of tissue factor at sites such as atheromatous plaques in patients with ischemic heart disease might precipitate clinically relevant coagulation and thrombosis. However, time and experience suggest that initial worries of severe, widespread thrombosis were slightly alarmist, and more recent studies have tended to use rather larger doses. This has culminated in the study conducted by Boffard and coworkers [48] in blunt and penetrating trauma, in which investigators used a large initial dose of 200 μg/kg followed by two further doses of 100 μg/kg in an attempt to manage bleeding in patients with traumatic bleeding requiring transfusion of 8 units of RBCs before administration of rFVIIa. The rationale for selecting this large dose was that it would provide serum concentrations of rFVIIa that Hedner and her colleagues felt from animal studies would be required to ensure (maintain) maximal coagulation from the effect of rFVIIa [3]. Further studies may determine whether more judicious use of rFVIIa is appropriate. An investigation into rFVIIa in prostatectomy [29] found good results with just 20 μg/kg and very good results with 40 μg/kg, and many of the case reports describe good results with around 80–90 μg/kg – the sort of dose used in management of hemophillia. It would seem prudent at this stage, until more safety studies have been completed, to consider doses in the range 40–80 μg/kg; the lower dose may be increased if appropriate in many acute use settings where there is no definitive body of evidence to direct practice.

A number of practical issues arise when using rFVIIa in acute management of hemorrhage, such as wastage of product once vials are opened, difficulties and/or unavailability of blood bank supplies, and inability to optimize all acute patients to achieve an ideal coagulation profile before administration of rFVIIa. Therefore some transfusion services have developed recommendations for rFVIIa based on the clinical condition, utilizing vial based dosing algorithms [49], such as the use of a 1200 μg vial and follow up with vitamin K therapy in cases involving prolonged INR with minimal bleeding or a 4800 μg vial for uncontrollable hemorrhage, in 50 to 100 kg adult patients unresponsive to more standard initial therapy [49]. In addition, rFVIIa may be useful in patients who urgently require FFP but have clinically documented significant IgA deficiency, in severely HLA-alloimunized thrombocytopenic patients who lack commonly available donors or in patients with rare RBC types or with multiple red cell alloantibodies who are undergoing surgery and other invasive procedures, in whom standard blood product transfusion may be ineffective or dangerous. In these cases, practicality and cost profiles change, and treatment may be necessary in the absence of the usual standard therapies.

Safety profile

Clinical experience with rFVIIa suggests that this treatment has a safety profile that favors overall efficacy in a variety of clinical settings. However, any concerns about use of the product should be addressed whenever possible during consultation with a hematologist. Few patients would be expected to experience allergic reactions to the components of rFVIIa, and through laboratory monitoring and close assessment of patients it should be possible to identify cases and signs of any resultant adverse events during use of this treatment. The most appropriate form of monitoring of rFVIIa is a topic of continued debate (see the review by Pusateri and Park in this supplement), because some laboratory measures of rFVIIa activity have not been found to correlate closely with clinical outcomes, and therefore often serve as a guide as to whether treatment has indeed been effectively dosed or are used to provide some insight into whether coagulopathies are indeed responsive to rFVIIa therapy. Thromboelastography may offer insights and correlate with rFVIIa effects [50] and has been used in clinical studies in which liver transplant patients were given rFVIIa [51].

Although patients with DIC have been excluded from receiving rFVIIa in prior studies, rFVIIa was recently specifically used in patients with DIC and associated hemorrhagic episodes. In this setting it was found to be effective in normalizing PT and activated partial thromboplastin time, and in controlling bleeding, without causing thromboemolic complications [52]. In a study of 18 patients with malignancy and bleeding secondary to DIC, administration of 3–10 doses of rFVIIa 90 μg/kg was effective hemostatic treatment, which the authors suggest are encouraging results, supporting the cautious use of rFVIIa in hemorrhagic DIC patients who fail to respond to conventional therapy. Despite the promise of this initial study, current best practice should involve very cautious use of this agent in DIC, active thrombosis, vascular grafts with endothelial injury, or other conditions at risk for thrombotic sequelae.

Conclusion

A growing body of evidence suggests that there is a role for rFVIIa in the management of acute, nontraumatic hemorrhage associated with a wide variety of clinical conditions in cases where bleeding cannot be controlled by conventional medical and surgical means. The ultimate safety, and the most appropriate and effective dose to employ in different patient groups are not well established. At present there is a large number of anecdotal case reports but only a few randomized, double blind, placebo controlled studies to provide evidence of this agent's efficacy outside its licensed indications. A number of studies have not demonstrated significant efficacy,

and there is a need for large scale safety studies to ensure that thromboembolic events do not become a major cause of morbidity. However, through close consultation with a hematologist, it should be possible to determine which patients might benefit from this hemostatic agent, and – as clinical studies with rFVIIa continue to report – the value of this treatment in both trauma and nontrauma settings will be established.

Competing interests

The author(s) declare that they have no competing interests.

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