Review Article

Recombinant factor VIIa

An update on its clinical use

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Summary

Recombinant activated factor VII (rFVIIa, NovoSeven®) has been successfully used to treat bleeding episodes in patients with antibodies against coagulation factors VIII and IX. In recent years, rFVIIa has also been employed for the management of uncontrolled bleeding in a number of congenital and acquired haemostatic abnormalities. Based on a literature search, this review examines the current knowledge on therapy with rFVIIa, from the now well-standardized uses to the newer and less well-characterised clinical applications.

Introduction

Recombinant activated factor VII (rFVIIa, NovoSeven, Novo Nordisk, Denmark) was originally developed for the treatment of hemophiliacs with inhibitors and then used successfully for treating haemorrhages in patients with acquired haemophilia (1–6). In the last few years, rFVIIa has also been utilized with benefit as a "universal haemostatic agent" in many other non-haemophilic bleeding situations including congenital factor VII deficiencies, quantitative and qualitative platelet disorders, hepatic failure, liver transplantation, surgery and trauma (7–12).

In this review, we briefly analyze the clinical experience regarding rFVIIa treatment, focusing particularly on the newer uses. Data were identified by searches of the published literature, including PubMed, references from reviews and abstracts from the most important meetings on this topic. Table 1 reports the current clinical applications of rFVIIa.

Mechanism of action of rFVIIa

Factor VIIa is an important contributor to the initiation of haemostasis (12). In fact, according to a cell-based model of coagulation (13, 14), following injury to the vessel wall, tissue factor (TF) is exposed to circulating blood and TF-FVIIa complexes are formed on the TF-bearing cells, where they activate factor X (FXa), leading to the conversion of prothrombin to thrombin. The limited amount of thrombin formed activates factors V, VIII and XI, as well as platelets, which in turn change shape and expose negatively charged phospholipids, such as phosphatidylserine. These activated platelets provide the template for further FX activation and full thrombin generation with a positive feedback on factors V, VIII and XI (15, 16). The extra thrombin formation results in the activation of thrombin-activable fibrinolysis inhibitor (TAFI), which protects the fibrin clot from premature lysis by down-regulating fibrinolysis (17). In summary, a full thrombin burst is essential for the formation of a stabile fibrin haemostatic plug that is resistant to premature fibrinolysis. In fact, in haemophilia only an initial, limited amount of thrombin dependent on the TF-FVIIa is generated, which is insufficient to consolidate and sustain the fibrin plug (18). In a cell-based *in vitro* model, it has been shown that the addition of increasing amounts of rFVIIa (between 50 and 150 nm) to activated platelets in the presence of factor X produces a linear increase of generation of factor Xa independently of the presence of TF on the platelet surface (15, 19–21). This dose-response mechanism can lead to the generation of significant amounts of thrombin even in the absence of factors VIII and IX, thus explaining the mechanism of action of rFVIIa in haemophiliacs (12). The direct activation of FIX on activated platelets in the absence of TF, resulting in improved thrombin generation, may also explain the mechanism of action of rFVIIa in acquired coagulopathy following trauma, surgery or other events (22). Moreover, the binding of rFVIIa to activated platelets may explain why rFVIIa is localized only to the site of bleeding (12, 14). However, other mech-

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Table 1: Clinical applications of recombinant activated factor VII.

Currently approved indications
1. Treatment of bleeding episodes and/or prevention of surgery-related bleeding in:
• Patients with FVIII or IX inhibitors
• Congenital factor VII deficiency
• Glanzmann thromboasthenia
Currently "off-label" applications
1. Treatment of bleeding episodes and/or prevention of surgery-related bleeding in:
• Platelet disorders (qualitative and quantitative)
• Liver disorders (cirrhosis, liver transplantation, fulminant hepatic failure)
• Surgery and trauma
• Other conditions (type III von Willebrand disease, factor XI deficiency, Jehovah's witnesses, bone marrow transplantation, hematologic malignancies, reversal of warfarin therapy, central nervous system bleeding, neurosurgery, preterm neonates, burns, uremic bleeding).

anisms of actions of rFVIIa have been proposed (23). In fact, ten Cate and colleagues first and van't Veer and coworkers successively proposed a TF-dependent mechanism of action of rFVIIa (24, 25). This model was more recently strengthened by Butenas and colleagues who reported that the local function of rFVIIa was mediated by the combined effect of TF expression and platelet accumulation at the site of a vascular lesion (26, 27). Lisman and De Groot recently analyzed the experimental data available and concluded that both the proposed mechanisms of actions of rFVIIa (i.e., TF-dependent and TF-independent) are plausible (23). In fact, if the TF pathway is usually required for the action of rFVIIa, a rFVIIa-mediated thrombin generation can also occur on the activated platelet surface independently of TF. Moreover, the same authors observed that the enhanced thrombin generation from rFVIIa not only accelerates clot formation, but also inhibits fibrinolysis by TAFI activation (28). In conclusion, according to current knowledge, rFVIIa induces haemostasis by enhancing thrombin generation on thrombin-activated platelet surfaces, thereby providing the formation of a stable, tight fibrin clot which is resistant to premature fibrinolysis.

Use of rFVIIa in haemophilic patients with inhibitors

Thanks to its ability to bypass the intrinsic coagulation pathway by activating factor X directly, independently of the presence of FVIII or FIX, recombinant activated factor VII has dramatically changed the treatment of haemophilic patients with inhibitors, thus permitting previously contraindicated major surgery (e.g. orthopaedic operations) (29). After the first report in 1988 of an open knee joint synovectomy successfully managed with rFVIIa (30), many other elective major surgical procedures have been performed in haemophiliac with inhibitors.

In a prospective, double-blind study published in 1998 on haemophilic patients with inhibitors undergoing surgery, Shapiro and colleagues demonstrated that rFVIIa, at a dose of 90 µg/kg, is an effective first-line option (31). Another randomized, double-blind multicenter study conducted in 1998 by the rFVIIa Study Group showed the efficacy of rFVIIa in treating joint,

muscle and mucocutaneous bleeding episodes in patients with inhibitors against factor VIII or IX (32). In the same year, a study on home-treatment with rFVIIa of haemophiliacs with inhibitors showed that a mean of 2.2 injections of 90 µg/kg at 3-hour intervals was effective at controlling mild to moderate bleeding episodes (33). The importance of early intervention during home treatment with rFVIIa shown in this study was further outlined by Santagostino and colleagues in a subsequent report evaluating a total of 53 bleeding episodes in patients with high-titer FVII inhibitors (34). Effective home treatment, achieving haemostasis in most patients after 2–3 bolus injections, was also reported by other groups (35, 36).

The dosing schedules of rFVIIa must take into account this agent's short half-life (approximately 2.9 hours), which necessitates frequent bolus injections (5). All published studies show that treatment with rFVIIa can be effective at doses between 35 and 120 µg/kg (5), independently of the inhibitor titer, with the standard recommended dose being 90 µg/kg given as a bolus and repeated after 2 hours. When more than 2 doses are necessary to ensure and maintain haemostasis in uncomplicated bleeding episodes, the dose-interval may be prolonged to every 4 hours for 1–2 days and every 6 hours until discontinuation, depending on the size and severity of the bleed. In surgical cases or complicated bleeds the rFVIIa must be administered every 2 hours for the first 24 hours and then the interval gradually lengthened (from 2 to 6 hours in the next 3 days) depending on the type of surgery (5, 11, 37). In most of the surgical trials reported in literature, rFVIIa was given in association with antifibrinolytic therapy (38–40).

In order to optimize doses, many groups have considered administering the rFVIIa by continuous infusion (41–54). A commonly utilized continuous infusion regimen includes an initial bolus dose of 90–180 µg/kg followed by continuous rFVIIa administration at a rate of 10–50 µg/kg/h (36). However, the results are still controversial: a broad range of doses has been utilized and the percentages of efficacy vary considerably (between 63 and 100%) in the different studies (55). Moreover, a clear correlation between the doses utilized and the haemostatic efficacy is not always present (43, 49, 51). Studies are currently evaluating the optimal dose for continuous infusion. In our opinion this route of rFVIIa administration might be beneficial for prolonged treatment and for surgical procedures. One recent study compared a continuous-infusion protocol versus the administration of a single-bolus "mega-dose" of rFVIIa (300 µg/kg) (56) and found that efficacy was higher, resolution of haemarthrosis quicker and rFVIIa consumption lower with the latter schedule. Studies are evaluating the efficacy and safety of rFVIIa "mega-bolus" as treatment for mild/moderate haemorrhages. The results of these trials will contribute to improving the clinical management of haemophiliacs with inhibitors, in particular paediatric patients who usually require higher doses of rFVIIa due to the higher clearance and shorter half-life of the drug in this age group (37, 57).

As regard to laboratory methods for monitoring rFVIIa therapy, measurements of post-injection prothrombin time (PT) and factor VII activity (FVII:C) have been suggested, although adequate haemostatic levels have not been defined (58). Recently, an alternative haemostatic laboratory method (the thromboel-

astogram) has been proposed (59, 60). However, to date no assay has been developed whose results correlate adequately with clinical outcomes in a sufficiently large sample of patients.

Use of rFVIIa in acquired haemophilia

After the first successful experiences with rFVIIa in the treatment of haemophilic alloantibody inhibitors, some centres experimented this drug in sporadic cases of acquired haemophilia (AH) with positive results (61–68). In a multicenter retrospective study, Hay and colleagues (69) described the results of rFVIIa treatment of hemorrhages in 38 patients with acquired haemophilia. A good response was noted in all 14 bleeds for which rFVIIa was used as first-line therapy. In the 60 bleeding episodes in which rFVIIa was administered as salvage therapy, the response was good in 75%, partial in 17% and poor in 8% of cases. The conclusion of the analysis was that rFVIIa is a safe, useful and effective treatment for bleeding in patients with acquired haemophilia. Recently, Baudo and colleagues (70) reported the data collected from the Italian Registry of Acquired Hemophilia: bleeding was controlled in 90% of the 20 cases in which rFVIIa was used (in 19 cases as first-line therapy and in 1 case as salvage treatment), thus suggesting the drug's efficacy in this condition.

Use of rFVIIa in congenital factor VII deficiency

Factor VII deficiency is a rare coagulation disorder that is characterised by spontaneous bleeding episodes in severely affected patients and bleeding after surgical procedures or trauma in mildly affected ones (71). Historically these patients were treated with fresh frozen plasma or prothrombin complex concentrates (PCC) (71). The development of plasma-derived FVII concentrates represented a substantial improvement in the management of FVII deficient patients (72, 73). Recent evidence (74–77) on the efficacy of recombinant FVIIa (NovoSeven) in the treatment of bleeding episodes in patients with congenital factor VII deficiency has allowed the drug's registration in Europe for the treatment of this rare coagulation defect. In a randomised study, Mariani and colleagues (75) reported the results of 17 FVII-deficient patients who were treated with rFVIIa for 27 spontaneous bleeding episodes, 7 major surgical operations and 13 minor interventions. They found that a mean dose of 22–26 µg/kg of rFVIIa was sufficient in all patients for effective haemostasis in these situations. Thus, according to this and other similar evidence (78, 79), the most effective dosage for rFVIIa replacement therapy in congenital FVII deficiency can be considered 20–25 µg/kg. Finally, successful prophylactic treatment of severely FVII-deficient patients with rFVIIa, given two to three times a week, was recently described (80, 81). A possible explanation of this phenomenon, apparently paradoxical given the short half-life of rFVIIa, is that the post-infusion levels of FVII are able to generate the necessary thrombin burst required to maintain haemostasis in these patients (80).

Use of rFVIIa in platelet disorders

The haemostatic effect of pharmacological doses of rFVIIa seems to be that of enhancing the rate of thrombin generation on thrombin-activated platelet surfaces, thus providing the thrombin necessary for the formation of a stable fibrin haemostatic plug (6, 23). Based on this information, rFVIIa has been employed in disorders characterized by impaired thrombin generation, such as quantitative and qualitative platelet defects (82–95). Kristensen and colleagues (84) studied 74 patients with moderate to severe thrombocytopenia due to impaired platelet production or immune destruction to evaluate the effect of rFVIIa administration. Given at a dose of 50 or 100 µg/kg, rFVIIa shortened the Ivy bleeding time in approximately 50 percent of the patients and all the 8 patients with overt bleeding had a clinical benefit from rFVIIa administration. No further results of clinical trials have been published since then and only case reports have appeared in the literature (85, 86).

As regards to inherited thrombocytopenia, rFVIIa was reported to enhance local fibrin deposition as well as partially restore platelet aggregates in Glanzmann thromboasthenia (GT) and Bernard-Soulier syndrome (BSS), conditions characterized by impaired thrombin generation (83). These data supported the use of rFVIIa as a potential haemostatic agent in such conditions. Recombinant factor VIIa was reported to stop or prevent bleeding in patients with Glanzmann thromboasthenia with or without antibody to GP IIb-IIIa (87–94). Poon and colleagues (88) successfully used rFVIIa to treat 24 bleeding episodes and to prevent bleeding during surgery in 4 children with GT, administering 89 to 116 µg/kg every 2 hours in association with antifibrinolytic drugs. In contrast to the above reports of success, Almeida and colleagues (95) found that rFVIIa was less satisfactory in the management of 28 acute bleeds and 5 surgical interventions in 7 children with inherited platelet function disorders (5 GT, 1 BSS and 1 storage pool disease [SPD]). Most children received 3 doses of 100 µg/kg of rFVIIa at 90-minute intervals and tranexamic acid. While the patients with BSS and SPD responded well to rFVIIa therapy, children with GT had variable results with an excellent or good response during surgery or when the severity of bleeding was mild and a poor or ineffective response in severe bleeding episodes. Peters and colleagues (96) reported on a 5-year-old boy with BSS and severe epistaxis not responsive to standard therapy who was successfully treated with rFVIIa. Finally, a patient with pseudo von Willebrand disease was reported to have been treated effectively with rFVIIa (97).

An international registry has been established in order to obtain more data on the safety, efficacy, optimal dose and interval of rFVIIa administration in inherited platelet disorders; data collection is continuing and updates are published periodically (90, 98).

Use of rFVIIa in liver disorders

Bleeding complications are a common cause of morbidity and mortality in patients with liver disease. Bleeding sources include gastrointestinal, variceal and intracerebral vessels. The coagulopathy of liver disease is multifactorial. Decreased synthesis of vitamin K-dependent coagulation factors (particularly factor VII, protein C and protein S), increased fibrinolysis and thrombocytopenia may all play a role (99). Traditional therapies include vitamin K, fresh-frozen plasma (FFP), desmopressin and platelets (99, 100). Limited data are available in the literature as

regards the haemostatic effect of rFVIIa for the treatment of bleeding in patients with liver disease (8). Moreover, a wide range of dosages (between 5 to 120 mg/kg) have been applied in the different studies, thus making any comparison of results difficult (100). A preliminary trial conducted by Bernstein and colleagues in 1997 (101) found that rFVIIa transiently corrected prolonged PT in a group of non-bleeding cirrhotic patients. A multicenter, randomized, double-blind trial investigated 71 patients with advanced liver disease undergoing laparoscopic liver biopsy under the cover of rFVIIa. These patients were randomized to receive one of four doses of rFVIIa (5, 20, 80 or 120 μg/kg); 48 (74%) of 65 patients achieved haemostasis within 10 minutes (102). The authors concluded that this procedure, otherwise contraindicated due to the coagulopathy, could be performed safely in such patients thanks to the use of rFVIIa. The European Study Group on rFVIIa in Upper Gastrointestinal Haemorrhage recently published (103) the results of a randomised, double-blind trial on the use of rFVIIa in 245 cirrhotic patients with upper gastrointestinal bleeding in which the patients were randomised to receive 8 doses of 100 μg/kg of rFVIIa or placebo in addition to standard pharmacologic and endoscopic treatment. Although there was no significant difference between the 2 groups for the primary composite endpoint (failure to control bleeding, failure to prevent re-bleeding and death), there was a significant reduction in the composite endpoint among the patients with variceal bleeding and more severe liver disease who received rFVIIa. Other studies have examined the use of rFVIIa in patients with cirrhosis and active variceal bleeding (104–106). Two single centre, open label studies involving small numbers of patients have reported that rFVIIa is effective in controlling variceal bleeding when used as an adjunct to standard treatment (104, 105). In contrast, in a retrospective analysis of the NovoSeven extended-use registry, O'Connell and colleagues (106) found that 6 of the 8 patients who did not respond to rFVIIa had liver disease (3 acute bleeds and 3 liver transplants) with a complex coagulopathy. Recombinant FVIIa was also shown to be more effective than conventional therapy with plasma for treating coagulopathy in fulminant hepatic failure (107). Another situation in which excessive bleeding can occur is during orthotopic liver transplantation (OLT). There are reports that rFVIIa is safe and reduces transfusion requirements when administered immediately before starting a transplant in patients with severe coagulopathy (108–110). Kalicinski and colleagues (108) reported on 2 paediatric patients undergoing urgent liver transplantation for fulminant liver failure; conventional therapy with plasma and cryoprecipitate had failed, but the children were successfully treated with 100 μg/kg of rFVIIa prior to the transplant (one child received an additional intra-operative dose). In another small series, Hendriks and colleagues (109) reported on 6 adult patients undergoing liver transplantation for cirrhosis who received a single dose of 80 μg/kg of rFVIIa prior to skin incision. The authors noted that, compared with controls, these patients required significantly fewer red cell and FFP transfusions. However, one patient developed a post-operative hepatic artery thrombosis. These results were contrasted by the recent randomized multi-centre study conducted by Planinsic and colleagues (111), who reported no difference in peri-operative red cell or FFP transfusions in 83 patients undergoing OLT and who received a single prophylactic dose of 20–80 mg/kg of rFVIIa or placebo. However, additional prospective, randomized trials evaluating the efficacy of rFVIIa in OLT are needed. Until the results of these studies are available, the routine use of rFVIIa in this setting is not justified.

Use of rFVIIa in surgery and trauma

A number of haemostatic changes occur in patients subjected to extensive surgery with substantial bleeding or in patients with acute, severe trauma with profuse bleeding requiring multiple transfusions. These haemostatic changes result in defective thrombin generation (9, 112). In 1999, Kenet and colleagues first successfully used rFVIIa infusions to manage acute, life-threatening traumatic bleeding (113). Since then, many reports have been published on the use of rFVIIa in post-trauma (114–120), obstetric (121, 122) and surgical (123–133) patients. However, randomized, controlled trials in this field are scarce, most of the studies being reports of single cases or small series. Martinowitz and colleagues (114) reported on 7 massively bleeding, multi-transfused, coagulopathic trauma patients successfully treated with a median of 2 doses of rFVIIa ranging from 40 to 120 μg/kg. Recently, Mayo and colleagues (115) observed a reduction of blood transfusion requirements after the use of rFVII (2 doses of 90–120 μg/kg) in 13 patients with acute, uncontrolled life-threatening bleeding. Recombinant FVIIa was also used as a "last chance" in a case of pulmonary haemorrhage after major trauma, associated with coagulopathy, heavy transfusion requirement and multi-organ failure (118). Bleeding stopped, with resolution of the hemothorax, after 2 doses of 60 mg/Kg of rFVII. A prospective, double-blind randomised trial of rFVIIa (a single dose of 20 μg/kg or 40 μg/kg) versus placebo in 36 patients undergoing radical retropubic prostatectomy found that patients receiving rFVIIa had significantly and dose-dependently less total peri-operative blood loss than the placebo recipients (129). Similar conclusions were drawn by Lodge and colleagues (132) in a multicentre, double-blind, placebo-controlled study evaluating the haemostatic efficacy and safety of rFVIIa in 204 patients undergoing partial hepatectomy due to neoplasia who were randomised to receive pre-operative injection of either placebo or rFVIIa (20 μg/kg or 80 μg/kg), followed by a second dose 5 hours after surgery began if the anticipated surgery time exceeded 6 hours. Park and colleagues reported on 9 patients with coagulopathy who required urgent neurosurgery; these patients were treated pre-operatively with rFVIIa (40–90 mg/kg) and had no bleeding or thromboembolic complications (133). A number of studies have investigated the role of rFVIIa in cardiac surgery, which is often associated with profuse haemorrhage (124–128). Aggarwal and coworkers (120) reported on a series of 8 surgical patients with intractable bleeding, 6 of whom underwent cardiopulmonary bypass. Bleeding stopped after 90 μg/kg of rFVIIa in all but one patient who required a further bolus. Al Douri and colleagues (124) and Hendricks and colleagues (125) reported that a single dose of rFVIIa was an effective treatment for severe intractable bleeding in patients undergoing heart surgery. In a recent study, Karkouti and colleagues analyzed the outcomes of 51 cardiac surgery patients who received rFVIIa for intractable blood loss compared with 51

matched control patients and found that rFVIIa, at a dose of 35 to 70 µg/kg, was effective in reducing intractable haemorrhage after cardiac surgery (126). Other reports (127, 128) have described the efficacy of rFVIIa in controlling severe bleeding following implantation of mechanical cardiac assist devices. However, the safety of rFVIIa in cardiac surgery patients was questioned by Dietrich and Spannagl who claimed that, due to the hypercoagulable state following systemic TF activation during cardiac procedures, rFVIIa could be dangerous in such patients (134). In summary, the experience of rFVIIa use in trauma with excessive bleeding as well as in postoperative profuse bleeding seems to indicate that one or two doses of 20 to 120 µg/kg of rFVIIa can have a haemostatic effect. However, as reported above, these data have been generated mainly from anecdotal reports and controlled randomised studies are needed to assess the safety and efficacy of rFVIIa in these patients.

Use of rFVIIa in other conditions

There are reports on the use of rFVIIa in a great number of severe bleeding conditions (135–160). As regards inherited bleeding disorders, Ciavarella and colleagues (135) reported on 2 patients with type III von Willebrand disease and a von Willebrand factor inhibitor who were successfully managed with rFVIIa for dental procedures. Other case reports have described the successful use of rFVIIa in preventing surgical bleeding in patients with severe factor XI deficiency with or without inhibitors (136–139). A pilot study conducted by O'Connell and colleagues (140) on 14 patients with severe or partial factor XI defect undergoing surgical procedures demonstrated that the association of tranexamic acid and rFVIIa, given preoperatively at a dose of 90 µg/kg and then every 2–4 h for 2–13 doses depending on the type of surgery, is effective in preventing bleeding after surgical procedures in such patients.

Recombinant FVIIa has been successfully used for the management of severe haemorrhage in Jehovah's witnesses, who refuse blood transfusions on religious grounds (141–144). Tanaka and coworkers (144) described the successful use of 45–60 µg/kg of rFVIIa in 2 Jehovah's witnesses who bled after cardiac surgery.

Severe bleeding refractory to standard haematologic or haemostatic support is common in patients undergoing bone marrow transplantation. Blatt and colleagues (145) used rFVIIa (boluses of 90–270 µg/kg with subsequent doses of 90 µg/kg every 4–24 h for 3–14 days) for the treatment of severe haemorrhage in 3 transplanted patients; 2 of them had transient clinical responses.

De Fabritiis and colleagues (146) reported on the use of rFVIIa for the treatment of severe bleeding episodes in 7 patients with haematologic malignancies and thrombocytopenia: 2 complete responses, 3 partial responses and 2 failures were documented. Hicks and coworkers (147) documented the efficacy of rFVIIa for the treatment of diffuse alveolar haemorrhage following bone marrow transplantation.

Recombinant FVIIa has also been employed in the reversal of warfarin therapy in cases in which the administration of vitamin K alone was found to be insufficient (148–154). Warfarin is a coumadin anticoagulant used to treat or prevent primary and secondary venous and arterial thromboembolism. Through vitamin K antagonism, it induces low levels of vitamin K-dependent coagulation factors, in particular factor VII which has been shown to be the earliest and the most sensitive of the coagulation factors to be affected by oral anticoagulant therapy (8). Spontaneous haemorrhages occur in approximately 10–20 percent of individuals receiving oral anticoagulant therapy (6). The use of rFVIIa in the reversal of warfarin therapy was first described by Diness and colleagues in 1990 in an animal model (148). In 1998, a study (149) of 28 healthy volunteers who received warfarin to produce an international normalized ratio (INR) > 2, demonstrated that doses from 5 to 320 µg/kg normalised the INR for periods ranging from 12 to 24 h. A spontaneous nosebleed in a patient on warfarin with an INR of 2.9 was reported to have been successfully treated with 2 doses of rVIIa 80 µg/kg (150). In 2 uncontrolled case series, one of 13 patients with an elevated INR with or without bleeding (151), the other of 6 patients with central nervous system (CNS) bleeding during warfarin prophylaxis (152), rFVIIa (dose range 10–40 µg/kg and 15–90 µg/kg, respectively) rapidly corrected INR in all cases. In conclusion, rFVIIa at doses between 15 and 90 µg/kg has been shown to markedly shorten PT and improve haemostasis in patients with warfarin intoxication (12). However, as rFVIIa does not influence the other vitamin K-dependent clotting factors (factors II, IX and X) (151), only clinical assessment can be considered a reliable parameter to assess rFVIIa efficacy. On the other hand, the efficacy of rFVIII in such a situation further confirms the hypothesis that the "thrombin burst" generated on activated platelet surfaces is critical to the haemostatic success of this drug.

The documented efficacy of rFVIIa in the treatment of CNS bleeding in haemophilic patients with inhibitors (155) led to the extension of its use also to non-haemophilic patients with CNS bleeding. Tobias (156) reported the successful use of rFVIIa, after antifibrinolytics and FFP had failed, in the treatment of bleeding complications in 2 children undergoing posterior spinal fusion. In a recent randomised, double-blind, placebo controlled, dose-escalation trial (157), 48 subjects with intracranial haemorrhage were treated with placebo or rFVIIa (10, 20, 40, 80, 120 or 160 µg/kg). Although no positive effect on hematoma volume was observed with any dose of rFVIIa, there was no biochemical or clinical evidence of increased thromboembolic complications.

Recombinant FVIIa has also been employed in preterm neonates, a category of patients at particular risk of developing bleeding complications due to their frequent low levels of coagulation factor resulting in prolonged INR (9). Griesen and colleagues (158) estimated the effect of rFVIIa on INR in 16 preterm neonates, observing that the reduction in the INR was dose-dependent and was significantly better than that achieved with FFP.

Finally, other studies have documented the success of rFVIIa in controlling bleeding in patients with extensive burns (159) or uremia (160).

Safety of rFVIIa

Relatively few adverse events have been associated with the use of rFVIIa in haemophilia and non-haemophilia settings (6, 37).

However, the primary concern regarding the safety of rFVIIa is its potential to induce thrombotic events (161, 162), considering the fact that, when administered at a pharmacological dose, the concentration of circulating rFVIIa is approximately 1000 times greater than normal (7, 163). Between 1996, the year in which rFVIIa was licensed, and April 2003, an estimated 700,000 doses of rFVIIa 90 μg/kg were administered to patients with congenital or acquired FVIII or IX inhibitors; the reported rate of serious adverse events was less than 1 percent (163). A similar rate of serious side effects was observed in a study by the Hemophilia Research Society of North America (HRS) on a total of 1939 bleeding episodes in 298 patients treated with rFVIIa (163). Isolated thrombotic events (myocardial infarctions, cerebrovascular accidents, venous thromboembolic events and cases of disseminated intravascular coagulation) have been reported in such patients in the last few years (163–165). However, most of the cases reported occurred in patients with coexistent risk factors (previous cardiovascular disease, advanced age) which may have contributed to the thrombotic event. Thrombotic complications following rFVIIa administration have also been described rarely in non-haemophiliacs. Bui and colleagues (166) described a death attributed to thrombosis in a lung transplant recipient with postoperative massive bleeding who had received rFVIIa and activated prothrombin complex concentrate (APCC). In a clinical trial on patients with factor XI deficiency undergoing surgery under cover with rFVIIa (90 μg/kg before and after operation), O'Connell (167) reported an acute cerebral vascular accident occurring in an elderly patient with a previous history of acute myocardial infarction. One of the 10 patients enrolled in a trial to prevent rebleeding after subarachnoid haemorrhage experienced cerebral artery thrombosis after receiving rFVIIa (168). D'Oiron and colleagues (169) reported on a patient with Glanzmann thromboasthenia who developed a thromboembolic complication that was attributed to the high continuous infusion rate of rFVIIa and the prolonged treatment period. Finally, Laffan and colleagues (170) reported 3 cases of thrombosis after rFVIIa treatment in 40 patients at high risk of thrombosis, thus concluding that this drug is safe and effective in patients without a preexisting coagulopathy. It should be mentioned that there are no reports of thrombotic complications of rFVIIa high-dose regimens (163).

Overall, the evidence reported in the literature indicates that rFVIIa is a safe way of inducing hemostasis in patients with defective thrombin generation; its thrombotic risk is lower than that observed with other clotting factor concentrates with known thrombogenic potential, such as APCC (31, 163, 171, 172).

Conclusions

From the analysis of the literature data, it appears clear that rFVIIa is a well-established, safe and effective treatment for patients with FVIII or IX inhibitors, congenital factor VII deficiency and Glanzmann thromboasthenia. In the last few years, along with the clarification of its mechanism of action, rFVIIa has been successfully employed in a great number of critical bleeding situations characterised by impaired thrombin generation. However, very few randomized, double-blind, placebo-controlled trials have been conducted so far and most of the published studies are reports on single cases or small series. Larger, randomized, controlled trials are needed in order to assess the efficacy, safety and dosage of rFVIIa in these newer "off-label" clinical applications.

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