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REVIEW

“Off-license” use of recombinant activated factor VII

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Summary Recombinant factor VIIa (rFVIIa) has been widely used in the treatment of bleeding episodes in haemophilic patients with inhibitors. In haemostatic circles it has also been assessed in reversing oral anticoagulant therapy. Over the last few years, it has been used “off-label” in patients with uncontrolled bleeding due to haemostatic abnormalities due to trauma and/or massive blood loss, thrombocytopenia, platelet dysfunction or liver dysfunction. This review examines the proposed mechanism of action of rFVIIa in the context of current concepts of haemostasis and its pharmacological properties. The “off-license” use of rFVIIa is reviewed. The latter are reported mainly as case reports, case series. There is an overwhelming need for randomized controlled trials to assess rFVIIa's efficacy, dosing and safety in current “off-license” use.

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Introduction

Recombinant activated factor VII (rFVIIa) was originally developed as a treatment for bleeding episodes in haemophilic patients with inhibitors to factor VIII or IX. In these patients there is safety and efficacy data. However, more data are still required to establish the most appropriate dose, and monitoring is difficult because no laboratory parameter has as yet been shown to equate with clinical effect.

Recently rFVIIa has been used as an “off-license” treatment in patients requiring rapid reversal of oral anticoagulation. It has also been used in uncontrolled bleeding due to haemostatic abnormalities due to trauma and/or massive

blood loss, thrombocytopenia, platelet dysfunction or liver dysfunction. These case reports and case series suggest that its efficacy may be applicable to bleeding in a wider patient population and have generated great excitement. However, the body of evidence for its use in these areas is mainly low grade, coming from case reports, case series and, more recently, a few small randomized trials.

There is a widely expressed need to find a life saving “magic bullet” in patients with uncontrolled bleeding. From the available evidence, rFVIIa appears to be an attractive option, but its safety, appropriate dosing and risk-benefit analysis are far from clear. If it proves to be an effective therapy for some patients with intractable bleeding, it would be welcomed, especially as its use would reduce the risks associated with allogeneic blood components, most notably transfusion-associated infections. However, as this paper will review, there is currently not enough evidence to fully

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establish its efficacy. Moreover, the unquantified risks of thrombosis, particularly on a tissue factor bearing atherosclerotic plaque, remains a concern. Last, at current prices, the use of rFVIIa has major resource implication.

The initial aim of this paper was to produce a systematic review of the use of rFVIIa, but on close inspection this is a premature exercise in view of the low grade of clinical evidence currently available. We have attempted instead to review the major papers and series produced in each area (if they exist), in order to illustrate the range of situations in which rFVIIa has been used, and to emphasize the uncertainty about efficacy, dosage and timing of use. The current concepts of coagulation and bleeding diatheses are reviewed first in order to explain our current understanding of the mechanism of action of rFVIIa.

Current concepts of haemostasis

The traditional view of the coagulation pathways as two linear pathways, the intrinsic and extrinsic, leading through the common pathway to the generation of thrombin and then fibrin from fibrinogen is now outmoded. The current scheme of physiological coagulation has undergone extensive revision and is dependent on the generation of tissue factor. Tissue factor is not normally in contact with plasma. If a vessel is cut, then sub-endothelial tissue factor is exposed to the blood flowing over it and notably factor VII. Factor VII (FVII) is present as a zymogen in circulating blood. It is unusual among coagulation factor zymogens in that it appears to have small degree of proteolytic activity before the liberation of an activation peptide and conversion to the active two-chain form (VIIa). However, minute amounts (10–100 pmol/l, i.e., approximately 1%) of FVIIa are detectable in the plasma.¹ These molecules avidly bind exposed tissue factor generating a membrane-bound complex. When associated with tissue factor, the activity of FVIIa is increased by a factor of 10^7 . The FVIIa–TF complex binds and activates factors X and IX. The factor Xa (FXa) formed is able to generate a small amount of thrombin locally. As FVIIa is such a poor activator of FX when not associated with TF², high concentrations of circulating rFVIIa would, therefore, only provide a haemostatic function at sites of tissue factor exposure.

Continuation of activation appears to be crucially dependent on the generation of activated platelet membranes on which pro-coagulant enzyme complexes form and mediate an explosive generation of thrombin. A check is kept on the

system by the initiation of negative feedback loops involving the physiological anticoagulants, tissue factor pathway inhibitor (TFPI), antithrombin and the activation of protein C.

These reactions are slow and inefficient, but once the constituent activated factors are present, an *amplification* phase occurs via the interaction of platelets in the vicinity of the damaged vessel wall. These become activated by thrombin: a conformational “flip-flop” of their membranes results in negatively charged phospholipids moving from the inner aspect of the membrane to the surface. Once activated, the platelets degranulate, releasing factor V amongst other substances. The activated platelet membrane provides the ideal environment for the generation of highly efficient pro-coagulant enzyme complexes operating at rates up to a million times faster than the individual serine proteases.² The first of these, a ‘tenase’ formed from factors IXa and VIIIa (FIXa/FVIIIa), rapidly generates FXa from its precursor. Its role in FXa production eventually supersedes that of the TF/FVIIa complex because it is up to 50 times more efficient and because a specific inhibitor of the TF/FVIIa complex steps in to shut the extrinsic pathway down. Another complex, ‘prothrombinase’, is made up of FXa and factor Va (FVa) and generates thrombin rapidly. Amplification occurs by the completion of a positive feedback loop when thrombin activates factor XI². Factor XIa (FXIa) generates FVIIIa (via the intrinsic pathway), thus fuelling production of further tenase complexes and hence, more thrombin.

The *propagation* phase sees a shift of location for the generation of thrombin from the TF-bearing cell surface to the surface of recruited platelets. The extrinsic pathway, in the physical form of TF/FVIIa complexes, is shut down by the action of tissue factor pathway inhibitor (TFPI). This binds TF/FVIIa and blocks its enzyme activity. The majority of the thrombin is generated in this phase by continuous activation of the tenase and prothrombinase complexes on the surface of recruited platelets.

Thrombin generated in the propagation phase activates factor XIII. This is required for the cross-linking of fibrin strands. This high concentration of thrombin activates thrombin-activatable fibrinolysis inhibitor (TAFI), as does FXIa. TAFI down-regulates fibrinolysis by modifying the interaction of plasminogen with fibrin. The actions of FXIIIa and TAFI in the presence of high thrombin concentrations generate a less permeable clot, which is resistant to fibrinolysis. The importance of the contribution of FXIa is seen in patients with a bleeding diathesis due to FXI deficiency. They have

an increased tendency to bleed from tissues with a high rate of local fibrinolysis, e.g., the urinary tract and oral cavity.³

It has been suggested that deficiency of FVIII or FIX limits generation of thrombin to the initiation and amplification stages.⁴ With a deficiency of FVIII or FIX, it is thought that a small amount of thrombin does form on the surface of the TF-bearing cell, but little is generated on the platelet surface itself. In order to activate platelets locally, the thrombin must diffuse to the platelet surface. This small quantity of thrombin and FXa generated are easily inhibited by antithrombin or TFPI before the propagation phase can occur. Thus, the overall thrombin generated is much less and fewer platelets are recruited. As a consequence, the clot generated under these conditions is more porous and susceptible to fibrinolysis. Similar deficiencies of thrombin generation are thought to exist in thrombocytopenia,⁵ disorders of platelet function, factor VII deficiency and the more general deficiency of vitamin K-dependent clotting factors seen in warfarin therapy and liver dysfunction. How rFVIIa overcomes this relative deficiency of thrombin is the subject of the following section.

Mechanism of action of pharmacological doses of rFVIIa

rFVIIa has proved effective in controlling bleeding episodes in haemophiliacs with inhibitors. However, the doses required (60–120 µg/kg 2 hourly) are much higher than those which generate a plasma concentration adequate for its binding to tissue factor.

The K_d for rVIIa binding to tissue factor is approximately 0.5 nM,⁶ while the concentration of rVIIa required for therapeutic efficacy is around two orders of magnitude higher.⁷ In this setting high doses of rFVIIa could overcome competitive binding of zymogen factor VII molecules to tissue factor.⁸ Alternatively, as considered in the past, it may be that tissue-factor rFVIIa is not the only initiator of coagulation, and certainly these findings suggest there tissue factor-independent generation of thrombin. It has been suggested that high dose FVIIa generates thrombin independently of tissue factor via a direct interaction with platelets.⁹ It has been demonstrated in vitro that FVIIa is able to weakly bind activated platelets ($K_D \sim 90$ nmol) and causes thrombin generation directly via activation of FX.^{10,11,4}

A cell-based model of clotting has been developed with monocytes expressing TF, platelets, clotting factors and calcium.⁹ The components of

the model have been manipulated to simulate various coagulopathies. In a FIXa-deficient system, addition of rFVIIa to concentrations of greater than 5 nmol/l restored thrombin generation.¹² This may be the mechanism by which rFVIIa operates in haemophiliacs. Certainly the concentrations of rFVIIa required in this model were similar to the predicted concentrations in haemophiliacs receiving clinically effective doses of rFVIIa. These findings were reinforced by more recent studies using phospholipid vesicles in an artificial mixture mimicking haemophilia B. Thrombin generation was restored to near normal by the addition of rFVIIa at a concentration of 10 nmol/l and in the presence of phospholipid surface.¹³

Kjalke et al.⁵ used the cell-based model to mimic thrombocytopenia in vivo. They manipulated the platelet density and concentration of rFVIIa, whilst observing platelet activation and thrombin generation. At physiological levels of FVIIa (0.2 nmol/l), the thrombin generation curve showed a lag phase, followed by a steep increase and then a gradual fall. By reducing the platelet density from 200 to 10×10^9 /l, they noted that the maximal rate of thrombin generation was reduced significantly. The experiments at lower platelet densities were then repeated with supraphysiological doses of rFVIIa. At these levels, the lag phase of thrombin generation was significantly reduced, though the overall maximal rate of thrombin generation was not affected significantly. The time to half-maximal platelet activation was also dramatically reduced (see Table 1). Indeed, the addition of high dose rFVIIa resulted in faster platelet activation at 20×10^9 /l platelets than in the physiological model, suggesting that a faster initial rate of thrombin generation and platelet activation allowed effective clotting despite low platelet numbers.

Combining all the experimental data to date, it maybe that rVIIa functions via a combination of tissue factor-dependent and tissue factor-independent pathways. These pathways result in enhanced thrombin generation, the consequences of which include increased activation of platelets, increased generation of TAFI, possible enhancement of Factor XIII activation as well as increased production of fibrin.

Characteristics of rVIIa

Recombinant FVIIa has an amino acid sequence identical to that of plasma derived rFVIIa and is produced from a baby hamster kidney cell line. The product is purified with the use of mouse monoclonal antibodies, treated to ensure viral inacti-

Table 1 Effect of rFVIIa on the lag phase of thrombin generation and time to half maximal platelet activation in thrombocytopenia-like conditions⁵

Platelet concentration (nmol/l)	Concentration rFVIIa (nmol/l)	Lag phase of thrombin generation (min)	Time to half-maximal platelet activation (min)
200,000	0.2	5.6 (3.7–6.9)	6.0 (3.9–8.2)
10,000	0.2	3.3 (0.7–5.4)	7.2 (4.1–12.0)
10,000	50	2.1 (0.0–4.8)	5.5 (3.5–11.9)
10,000	100	1.1 (0.0–2.3)	4.7 (3.4–8.2)
10,000	500	0.5 (0.0–1.5)	4.3 (1.4–6.8)

Values given as mean (range).

vation, and undergoes auto-activation to rFVIIa during ion exchange chromatography. Whilst the recombinant protein is manufactured without exposure to any human products, the cell line is cultured in bovine albumin. Thus, rFVIIa should not be used in patients with a known hypersensitivity to mouse, hamster or bovine proteins.

As expected, similar to the endogenous protein, rFVIIa has a short half-life ($t_{1/2}$), which varies among individuals, but is approximately 2.7 h after a single bolus in adults. It does not appear to differ in haemophiliacs, healthy volunteers or in patients with cirrhosis, but the half-life in children and in bleeding haemophiliacs appears shorter.^{14,15} As a consequence, the dosing interval in treating haemophiliac bleeding is 2-hourly, lengthened up to 4-hourly later in the course of treatment. In an attempt to provide more constant rFVIIa levels, the use of loading bolus followed by a continuous infusion of rFVIIa has also been investigated.¹⁶

Whilst the PT and APTT are shortened with pharmacological doses of rFVIIa, these do not appear to be direct correlates of its action. A major problem in the management of patients with rFVIIa is that there is no consensus as yet on the most appropriate assay with which to monitor treatment with rFVIIa. The measurement of FVII clotting activity (FVIIC) in the treatment of haemophiliac inhibitor-related bleeding has led to a recommendation of a minimum level of 6–10 IU/ml FVIIC activity and peak levels of greater than 30–50 IU/ml when giving IV boluses.¹⁷ In haemophiliac patients with inhibitors, a recent paper has suggested that good post-operative haemostasis can be achieved with continuous infusion of rFVIIa to provide a level of 30 IU/ml or more.¹⁸ Plasma FVIIa has also been measured directly via a one-stage clotting assay.¹⁹ There is some debate as to whether FVIIa and FVIIC levels can be used interchangeably^{20,21} for they show a predominantly linear relationship. More recently, the role of thromboelastography (TEG) in providing a near-patient test of clotting has been explored, partic-

ularly during liver transplantation and is worthy of further investigation as a near-patient assessment of efficacy.²² In providing information such as the rate of clot generation and physical characteristics of the clot formed, the TEG or a derivative the RoTEG or Rotem²³ may provide the nearest correlate of potential thrombin generation in the near-patient setting of rFVIIa therapy.

“Off-label” use of rVIIA

Reversal of over anticoagulation

Warfarin is the most widely prescribed oral anti-coagulant therapy and prolonged use for many years may be necessary, particularly for treating symptomatic hypercoagulability, chronic atrial fibrillation, maintaining mechanical prosthetic heart valves, and preventing acute myocardial infarction and stroke.²⁴ Unfortunately warfarin therapy has a narrow risk-to-benefit profile. Its complex pharmacokinetics is influenced by concurrent medications, ethanol ingestion, variability of vitamin K intake and absorption, and hepatic disease.²⁵ It is not surprising, therefore, that the most common complication of warfarin use is adverse bleeding.²⁶ For patients receiving warfarin, estimated yearly risks are 0.6% for fatal bleeding, 3.0% for major haemorrhage and 9.6% for minor events,²⁷ and the incidence of bleeding complications is directly proportional to the intensity of anticoagulation²⁸ and time spent at a high international normalized ratio (INR).²⁹ Various strategies have been used to reverse warfarin-induced excessive anticoagulation. In a patient with a prolonged INR without active bleeding but with an anticipated high risk for bleeding, the INR can be decreased slowly by administering an exogenous source of vitamin K₁.³⁰

Traditional treatments (fresh-frozen plasma, prothrombin complex concentrate) for rapid reversal of excessive anticoagulation from warfarin are limited by inconvenience and potentially

serious side effects, most notably of transfusion-transmitted infection.

Preclinical studies in rats³¹ and normal humans who ingested acenocoumarol³² have demonstrated the safety and feasibility of rFVIIa use in the clinical setting. Anecdotal reports have supported the potential effectiveness of rFVIIa for reversing warfarin-induced excessive anticoagulation to facilitate surgery.³³ In a study of healthy volunteers treated with a coumarin to a INR greater than 2, rFVIIa shortened the INR and elevated FVII: C levels for 12 h or more.³⁴ Deveras and Kessler al.³⁵ conducted a prospective study of rVIIa in patients receiving warfarin with critically prolonged INR and bleeding complications. The dose of rFVIIa administered was based on the patient's weight, rounded off to the closest vial size (1.2 and 4.8 mg). The first patient received 90 µg/kg of body weight, but subsequent patients were treated with progressively lower doses as it became apparent that even doses in the 15–20 µg/kg range provided adequate haemostasis. Recombinant FVIIa was administered intravenously over 3–5 min and immediately reduced INRs without adverse effects, regardless of rFVIIa dose (range, 15–90 µg/kg of body weight). Indications for use of rFVIIa included an INR greater than 10 in high-risk persons ($n = 5$), clinical haemorrhage ($n = 4$), and diagnostic or therapeutic procedures ($n = 4$), the type of range of problems seen in any district general hospital. Vitamin K-dependent coagulation proteins (factors II, VII, IX and X) were assayed in four patients 1 h before and 1 h after rFVIIa infusion. The activity of these proteins was markedly deficient, which is consistent with the effects of warfarin. As expected, the activity level of factors II, IX and X did not appreciably increase after rFVIIa treatment. However, FVII activity increased dramatically (by more than 500%). These results demonstrate efficacy for rVIIa in reversing warfarin but before changing treatment policy of rapid warfarin reversal on the basis of these preliminary findings, physicians should watch for controlled studies that compare outcomes, side effects and costs in patients treated with rFVIIa versus traditional therapies.³⁶

In addition, rFVIIa has been shown to reverse the anticoagulant effects of the selective factor Xa inhibitor fondaparinux in healthy volunteers.³⁷ In one part of the study, 10 mg of fondaparinux was administered subcutaneously 2 h before a single intravenous bolus of rFVIIa 90 µg/kg or placebo. Injection of rFVIIa (90 µg/kg) normalized the prolonged activated partial thromboplastin and prothrombin times and reversed the decrease in prothrombin fragments 1 + 2. Thrombin-generation time and endogenous thrombin potential, which

were inhibited by fondaparinux, normalized up to 6 h after rVIIa injection.

Thrombocytopenia

The efficacy of rFVIIa in controlling bleeding in moderate to severe thrombocytopenia has been studied in various clinical settings. Kristensen et al.³⁸ conducted a study in patients with thrombocytopenia due to bone marrow disorders or autoimmune destruction using single doses of 50 or 100 µg/kg rFVIIa. The bleeding time was little affected, being reduced by 2 min or more in only 55 out of 105 cases. This effect when it occurred was significantly more pronounced in patients with a platelet count of greater than $20 \times 10^9/l$, but was not dose-dependent. They also administered rFVIIa in doses of 50 or 100 µg/kg in 13 patients with platelet counts less than $30 \times 10^9/l$ and bleeding. Bleeding ceased in seven cases and slowed down in three; there was no clear correlation with shortening of the bleeding time. One patient had an anaphylactoid reaction. Apart from this study, there are no other large studies, but a number of case studies where rFVIIa was used in thrombocytopenic patients who had failed standard management of platelet transfusion. Table 2 shows three reports.

It is interesting that the doses used roughly correspond to the plasma concentrations of rFVIIa used in the cell-based model of thrombocytopenia.⁴ There, the rate of platelet activation was restored by supra-physiological levels of 50 nmol/l rFVIIa or greater. A dose of 100 µg/kg rFVIIa generates a plasma level of approximately 50 nmol/l (assuming 100% recovery). This would appear to correlate with the clinical effect seen above.

Gerotziakas et al.⁴⁰ also carried out *ex vitro* experiments on samples of blood taken from patients 2 and 3 before and after the administration of rFVIIa. They demonstrated a 200-fold increase in the FVIIa levels. Samples from both patients showed reduction in bleeding time, PT and APTT with rVIIa and impaired clot retraction, which normalized after the administration of rFVIIa but no increase was seen in the maximum level of thrombin.

Haemorrhagic complications, particularly bleeding from the gastrointestinal tract, reduce survival following bone marrow transplantation. Kaplan–Meier analysis of a group of 807 allogeneic haemopoietic stem cell transplantation indicates that the 10-year survival in patients suffering from haemorrhagic complications is 50% compared with 75% in patients who don't bleed. The severity of bleeding is reflective of the severity of graft-versus-host disease.⁴¹ A multicentre, randomized, double-blind trial is currently investigating the efficacy and safety of rFVIIa in the treatment of allogeneic

Table 2 Cases of thrombocytopenic bleeding treated with rFVIIa

Case	Age	Diagnosis	Transfusion requirements pre rFVIIa (U)	Bleeding source	Platelet count $\times 10^9/l$	Dose of rFVIIa mcg/kg	Haemostatic parameters pre/post-rFVIIa
1	27	Acute myeloid leukaemia	Platelets 16 (daily)	Subdural and peri-orbital haematomas haemoptysis, Epistaxis	<5	100	PT 16.9 s/not done
2	75	Waldenstrom's macro-globulinaemia	Platelets 18 Red cells 3		2	90	BT 25/18 min PT 12/8 s APTT 45/29 s
3	52	Acute lymphoblastic leukaemia	Platelets 15 Red cells 11 FFP 13	Upper gastro-intestinal tract	15	90	BT 15/7 min PT 16/8 s APTT 45/30 s

Abbreviations: BT, bleeding time.

Case 1.³⁹

Cases 2 and 3.⁴⁰

haemopoietic stem cell transplantation using three doses of rVIIa, aiming to recruit 100 patients by the end of 2003.⁴¹

Inherited platelet disorders

Patients with rare, congenital platelet defects have been described successfully undergone rFVIIa therapy before surgery or to treat bleeding episodes. These include disorders such as Glanzmann thrombasthenia (abnormal receptor glycoprotein IIb/IIIa),^{42,43,44} Bernard Soulier syndrome (abnormal glycoprotein Ib platelet receptor)⁴⁵ and von Willebrand disease.^{46,47}

Poon et al.⁴³ used rFVIIa to treat bleeding in 24 episodes and prevent bleeding during a bilateral herniorrhaphy in four children with Glanzmann thrombasthenia, using 89 $\mu\text{g}/\text{kg}$ top 116 $\mu\text{g}/\text{kg}$ per bolus injection every 2 h with antifibrinolytic drugs. Bleeding stopped in all cases but platelet transfusion was required in one. An International Registry on the use of rVIIa in congenital platelet disorders was established to obtain more data.⁴⁸

Almeida et al.⁴⁹ described their experience in using rVIIa on 33 occasions in seven children with inherited platelet function disorders. Five had Glanzmann's thrombasthenia, one had Bernard-Soulier syndrome and one had storage pool disease with a severe phenotype. They used a protocol of three doses of a minimum of 100 $\mu\text{g}/\text{kg}$ of rVIIa at 90-min intervals. Bleeding ceased in 10, with seven only requiring two doses. The two features that predicted response to rVIIa were the severity of the bleeding and the delay from the onset of bleeding to treatment. Five episodes of planned surgical intervention were treated successfully with rVIIa.

Eighteen of the 28 episodes required blood product support and there was no overall reduction in transfusion requirements. Pre- and post-PFA-100 showed no change in closing time with either the collagen/adrenaline or collagen/ADP cartridges.

Acquired platelet disorders

Whilst congenital platelet dysfunction is extremely rare, acquired platelet disorders are not. The use of rVIIa has been described in uraemia and increasingly iatrogenic causes due to the use of aspirin, clopidogrel and glycoprotein (GP) IIb/IIIa inhibitors in acute coronary syndromes. These cases are shown in Table 3.^{50,51,52}

Hepatic dysfunction

There are a multitude of haemostatic defects, which contribute to hepatic coagulopathy.⁵³ These include thrombocytopenia, impaired platelet function, reduced production of vitamin K dependent clotting factors, reduced hepatic clearance of tissue plasminogen activator (tPA) and excessive fibrinolysis. The reduced synthetic function and clearance of activated clotting and fibrinolytic factors in chronic hepatic dysfunction results in elevated levels of prothrombin fragments, D-dimers and thrombin-antithrombin complexes.⁵⁴ Patients with liver dysfunction usually have disproportionately low factor VII levels compared to the other vitamin K-dependent factors⁵⁵ and the prothrombin time is lengthened accordingly. Administration of vitamin K is usually not fully effective in reversing the prolongation of the prothrombin time due to hepatocellular dysfunction. Whilst administration of fresh frozen plasma

Table 3 Use of rFVIIa in acquired platelet dysfunction complicated by bleeding

Case	Age	Diagnosis	Bleeding source	Doses rFVIIa mcg/kg	Outcome
1	49	Acute renal failure, thrombocytopenia	Gastrointestinal, urinary tract, gingival, venepuncture sites	90	Bleeding stopped
2	12	Uraemia, cytomegaloviral pneumonitis	Pulmonary	90	Bleeding stopped
3	59	Acute MI, tirofiban (inhibits GP IIb/IIIa) administration post-PTCA and stenting	Epistaxis, oropharyngeal, gastrointestinal, pulmonary	84, 168	Bleeding slowed

Abbreviations: MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

Case 1 from Moisescu et al.⁵⁰

Case 2 from Révész et al.⁵¹

Case 3 from Stepinska et al.⁵²

may temporarily reverse the coagulopathy, a large volume is often required. This may cause fluid overload in the setting of hypoalbuminaemia and capillary leak. Patients with chronic liver dysfunction are further pre-disposed to bleeding by the development of varices. This carries a mortality of around 30% per bleeding episode.⁵⁶

The data that rFVIIa can correct the haemostatic defect caused by deficiency of vitamin K-dependent clotting factors led logically to its use in hepatic dysfunction. rFVIIa in a single dose of 5–80 µg/kg normalized the prothrombin time (PT) in 10 patients with coagulopathy secondary to advanced liver disease that were not actively bleeding,⁵⁷ and no adverse events occurred. rFVIIa also corrected the PT in cirrhotic patients known to be bleeding from oesophageal varices.⁵⁸ Ten patients with a mean initial PT of 18.1 s were treated with terlipressin, red cell transfusion and a single dose of 80 µg/kg rFVIIa. In all cases, the PT normalized for up to 4–6 h, and bleeding was controlled during the study period of 12 h. It is not possible to draw a conclusion on the clinical efficacy of rFVIIa as there was no control arm. In all, six patients died acutely as a result of their bleed. Of note, none of the patients had thrombotic complications.

The coagulopathy associated with hepatic failure results in a considerable risk of bleeding complications during procedures such as liver biopsy and surgery, including liver transplantation. rFVIIa has been used successfully in patients with liver dysfunction undergoing endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous liver biopsy that developed bleeding subsequent to their procedures.^{59,60} The role of *prophylactic* rFVIIa in cirrhotic patients undergoing invasive procedures has also been explored. rFVIIa was used at a dose of 5, 20, 80 or 120 µg/kg in 65 cirrhotic patients with a prolonged PT undergoing

laparoscopic liver biopsy.⁶¹ The PT was shortened to near normal or normal in all patients and 48 patients (74%) achieved haemostasis within 10 min. Thirteen patients (20%) required a further dose of rFVIIa for bleeding after 10 min, but none of these required any further intervention. The outcome of the remaining four patients was not reported. One patient suffered a portal vein thrombosis after receiving 5 µg/kg of rFVIIa. The group as a whole showed no significant difference in the laboratory markers of coagulation before and after the administration of rFVIIa. Again, the absence of a control arm makes it difficult to assess the overall clinical effect of rFVIIa in this setting.

A placebo-controlled, randomized and blinded study was carried out in 39 patients with hepatic coagulopathy (PT prolonged by 1–15 s and platelets 20–60,000/mm³) undergoing dental extractions. Prophylactic rFVIIa at either 20 or 80 µg/kg did not improve time to haemostasis, possibly because of a low incidence of prolonged bleeding in the control group.⁶²

In a multi-national, double-blind trial, 204 patients were given rFVIIa 920 or 80 µg/kg or placebo pre-operatively prior to undergoing partial hepatectomy for benign or malignant tumours. A reduction in blood loss and red cell transfusion was seen in those receiving rFVIIa. Preliminary analysis has shown that mean intra-operative blood loss was 1073 ml in the 80-µg/kg group compared to 1422 and 1372 ml in the placebo and 20-µg/kg group, respectively ($p = 0.068$). The proportion of patients requiring peri-operative red cells was 30% lower in the 80-µg/kg group (25%) relative to placebo (37%). There was no increase in post-operative thromboembolism.⁶³

One of the indications for liver transplantation in acute hepatic failure is a PT greater than 100 s.⁶⁴ This pre-disposes to significant operative bleeding risk, which in turn has an impact on outcome.

Indeed, the 3-month mortality rates in liver transplantation are related to transfusion requirements.⁶⁵ rFVIIa has been successfully used to correct haemostasis in two boys with fulminant hepatic failure undergoing orthotopic liver transplantation (OLT).⁶⁶ Transfusion of blood products had failed to stop active bleeding from the GI and urinary tracts in one child, or to correct pre-operative INRs of 5.7 and 6.9, respectively. Blood loss was considered minimal after rFVIIa. No thrombotic post-operative complications were seen in either child. Following this, a pilot study looked at the effect of a prophylactic, 80 µg/kg dose of rFVIIa in six patients with end-stage liver disease undergoing OLT, as compared to 10 controls. The results of the trial showed significantly lower blood component requirements in the study group and a significant reduction in peri-operative blood loss.⁶⁷ Markers of coagulation showed a sharp increase in thrombin generation after reperfusion with rFVIIa, suggesting that rVIIa during OLT was able to enhance thrombin generation in a localized and

time-limited manner without causing systemic disseminated intravascular coagulation.⁶⁷ A subsequent randomized, controlled and blinded trial was performed in 82 patients undergoing OLT. In this study a single prophylactic dose of 20–80 µg/kg rFVIIa made no difference to the peri-operative blood or FFP transfusion requirements.⁶⁷ There was no difference in the incidence of hepatic artery thrombosis between the placebo and treatment arms. Further, larger studies giving doses at various time points are currently in progress.⁶⁸

Uncontrolled bleeding due to trauma and surgery

At present the standard treatment for significant haemorrhage during surgery or trauma is the rapid control of the source of bleeding by either surgical techniques, packing or tamponading the bleeding area or ligation of major vessels supplying the bleeding area.

At the same time blood volume needs maintaining to allow for adequate tissue oxygenation.

Table 4 Effect of rFVIIa in treating gastrointestinal haemorrhage

Case	Age	Cause of bleeding	Transfusion requirement pre rFVIIa (U)	Coagulation parameters pre-/post-rFVIIa (s)	Dose rFVIIa (mcg/kg)	Transfusion requirement post-rFVIIa (U)	
1	22	Terminal ileal haemorrhage due to Crohn's requiring bowel resection	Red cells	PT 16/7.5 ^a	2 × 90	None	
				32			
			FFP	APTT 28.9			
			Platelets	38			
2	62	Lower GI haemorrhage due to colonic lymphoma	Red cells	PT 21/11.3 ^a	2 × 90	No red cells required	
				60			
			FFP	APTT 30.6			
			Platelets	60			
3	59	Duodenal ulcer requiring oversew, pyloroplasty, vessel ligation × 2	Red cells	PT and APTT within normal range	10 × 90	Red cells 7	
				65			
			FFP	?			
			Platelets	?			

Cases 1 and 2 from White et al.⁸⁷

Case 3 from Vlot et al.^{88a} Denotes mean value.

The use of high molecular weight colloids such as hydroxyethyl starches and dextrans can produce a pseudo von Willebrand's syndrome and interfere with the structure of clot formed.^{69,70} Haemostatic components also need replacing after massive blood loss and platelets, fresh frozen plasma and cryoprecipitate are used. Fibrin sealants and other pharmacological agents such as aprotinin and tranexamic acid may also be used. However, it is argued that there remains a need for an agent that will enhance local thrombotic processes, for failure to control massive bleeding will often lead to hypothermia, acidosis and a dilutional coagulopathy, which worsen the already precarious haemostasis. rFVIIa has been tried "off-license" as a rescue therapy in such cases. As yet there are no placebo-controlled randomized studies on the use of rVIIa in trauma and massive blood loss, but there are many case reports.

Kenet et al.⁷¹ described the first use of rFVIIa in life-threatening trauma bleeding. This was in a 19-year-old with a torn inferior vena cava injury due to a high velocity rifle injury. Despite the use of multiple blood components, the wound bled at a rate of 300 ml/min, and rFVIIa was given as a last resort in a dose of 60 µg/kg and blood loss slowed to 15–20 ml/min. A further dose of 60 µg/kg/h later stopped the ooze and produced normalization of coagulation tests. Surgeons were then able to operate.

Following a safety and efficacy study in pigs,⁷² Martinowicz et al.⁷³ presented a case series of seven patients with massive bleeding and transfusion requirements post-trauma in whom rFVIIa was used after all surgical and blood component therapy had failed in patients between June 1999 and January 2001. They included patients with gun shot wounds, blunt trauma following accidents and a victim of stabbing. All patients displayed evidence of coagulopathy despite multiple transfusions. They were then given rFVIIa at a dose of 40–120 µg/kg, followed by further doses up to a maximum of 3 (median number of doses 2; median total dose 120 µg/kg, 25th–75th interquartile range 120–212 µg/kg). The time from presentation to adminis-

tration of rFVIIa varied from 4 h to 31 days. Diffuse bleeding stopped in all cases, in some revealing bleeding from larger vessels, which was amenable to further surgery. The PT, PTT, FVII level and packed cell requirements were all significantly reduced (Table 5). Three of the seven patients died, the cause of death was considered unrelated to the use of rFVIIa. None suffered thromboembolic complications.

O'Neill et al.⁷⁴ presented a similar case, a patient with multiple stab wounds, resulting in a grade III liver injury. Despite transfusion of 108 U of red cell products, 78 U of FFP, 18 U of cryoprecipitate, 12 pools of platelets, three surgical explorations and two angiographic embolizations, massive liver haemorrhage continued in the setting of a prolonged PT and APTT. A single dose of 90 µg/kg rFVIIa was administered as a last resort. Bleeding stopped with correction of her PT, haemoglobin and metabolic indices. Further surgical interventions were undertaken without bleeding complications. The patient eventually died of candidaemia, a postmortem showed no evidence of thromboembolic complications.

rFVIIa has also been used as a last resort treatment in a case of pulmonary haemorrhage after major trauma, which was associated with coagulopathy, huge transfusion requirements and multi-organ failure. Bleeding stopped after two doses of 60 µg/kg rFVIIa, with resolution of the haemothorax, and the patient made a full recovery.⁷⁵

Since the use of rFVIIa in trauma was described, there have been case reports where rFVIIa has been used to treat uncontrolled post-operative bleeding. In two case reports^{76,77} 120 µg/kg of rFVIIa was used successfully to stop post-operative bleeding when the conventional treatment had failed. Bouwmeester et al.⁷⁸ have described one patient who received 60 µg/kg of rFVIIa after failure of ligation of internal iliac arteries, subtotal hysterectomy and packing of pelvis and blood components to control diffuse pelvic bleeding. The issue of assessing the use of rFVIIa in these types of situation is difficult. There are some case

Table 5 Coagulation parameters of trauma patients treated with rFVIIa From Martinowicz et al.⁷³

	Median (25–75th interquartile range)	
	Before rFVIIa	After rFVIIa (* denotes $p < 0.05$)
PT (s)	24 (20–31.8)	10.1 (8–12)*
PTT (s)	79 (46–110)	41 (28–46)*
FVII level (IU/ml)	0.7 (0.7–0.92)	23.7 (18–44)*
Packed cell requirement (U)	36.5 (25–50)	2 (1–2)*

reports where a critique of the paper would suggest that the appropriate use of haemostatic replacement had not been followed prior to the administration of rFVIIa, and that in such a settings it was being used to treat a dilutional coagulopathy. Ideally a randomized trial of best practice management of massive blood loss would utilize adequate haemostatic replacement with blood components and pharmaceutical agents such as fibrin sealant and aprotinin prior to using rFVIIa versus placebo as a "last ditch action". But is this ethical? Moreover, this is not an easy trial to perform. Massive blood loss is not a day-to-day occurrence and so a trial would be logistically difficult and require multiple centres. Moreover, it appears to the authors that one of the issues is the ability of units to provide "best practice" management of massive blood loss, when the fast accessibility of blood components may not be possible, e.g., when platelets might take an hour to reach a hospital from the Transfusion Centre. Should there be therefore a trial of best practice management versus rFVIIa in the management of a dilutional coagulopathy?

The use of rVIIa in cardiac surgery

The use of cardiopulmonary bypass is associated with a bleeding diathesis related to thrombocytopenia, platelet dysfunction, fibrinolytic activation, a dilutional coagulopathy and the need for heparinization of the circuit. Post-operative bleeding occurs in approximately 2.8%, necessitating re-exploration.⁷⁹ Aggarwal et al. reported a series of eight surgical patients with intractable bleeding, six of who had undergone cardiopulmonary bypass. Bleeding stopped with 90 µg/kg of rFVIIa in all except one patient who required a further bolus.⁸⁰ Table 6 summarizes the findings of a case series by Al Douri et al.⁸¹ and a case report presented by Hendriks et al.⁸². In all cases, control of bleeding was achieved after a single injection of rFVIIa. The study by Al Douri et al.⁸¹ excluded patients with a history of ischaemic heart disease. Tanaka et al.⁸³ describe the successful use of 45–60 µg/kg of rFVIIa in two Jehovah's witnesses who bled after cardiac surgery. Both patients had low levels of fibrinogen, platelets and abnormal coagulation screens. Interestingly there was improvement in thromboelastogram parameters in the presence of abciximab.

Table 6 Summary of the use of rFVIIa in cardiac surgery

Case	Procedure	Age (years)	Blood loss pre rFVIIa (ml)	Coagulation parameters pre rFVIIa	Dose of rFVIIa (mcg/kg)	Blood loss post-rFVIIa (ml)
1	Arterial switch, shunt closure, ASD repair, Le Compte manoeuvre	2.5	4500	FVII 0.3 IU/ml	30	85
2	MVR, tricuspid valve repair, re-sternotomy	73	5300	PT >20 s FVII 0.3 IU/ml	30	226
3	MVR, AVR, re-sternotomy for insertion of RVAD & IABP	48	1100	PT >20 s PT >20 s	30	240
4	Aortic valve and root replacement	66	5000	FVII 0.45 IU/ml	30	270
5	MVR, repair of right aorto-ventricular aneurysm	48	8000	PT >20 s FVII 0.21 IU/ml	30	414
6	Mitral and tricuspid valve repair, IABP insertion, re-sternotomy × 2	65	>1400	PT >20 s PT 27.2 s	90	350
				APTT 49.7 s		

Cases 1–5 from Al Douri et al.⁸¹; Case 6 from Hendriks et al.⁸²

Abbreviations: ASD, atrial septal defect; MVR, mitral valve replacement; AVR, aortic valve replacement; RVAD, right ventricular assist device; IABP, intra-aortic balloon pump.

Bleeding is common following implantation of mechanical cardiac assist devices. Two reports by Zietkiewicz et al.⁸⁴ and Potapov et al.⁸⁵ describe control of severe haemorrhage in two patients after implantation of ventricular assist devices that failed to respond to conventional therapy. rFVIIa was given to one patient in doses of 20 and 20 µg/kg and the other in doses of 120 µg/kg. Both dramatically reduced bleeding, and importantly in patients with mechanical assist devices there were no thromboembolic complications.

Preventing peri-operative bleeding

A randomized controlled trial of the use of rFVIIa in preventing peri-operative bleeding was carried out in patients undergoing retro-pubic prostatectomy.⁸⁶ This was a double-blinded study of 36 patients randomized to receive a peri-operative dose of 20 or 40-µg/kg rFVIIa, or placebo. The peri-operative blood loss, haemoglobin, coagulation parameters and duration of surgery were followed. Median blood loss was 1235 ml (IQR 1025–1407) and 1089 ml (928–1320) in groups given rFVIIa 20 and 40 µg/kg, respectively, compared with 2688 ml (1707–3565) in the placebo group ($p = 0.001$). No patients receiving the higher dose of rFVIIa required transfusion. There were no adverse events in the study group. This study suggests rFVIIa if proven to have a good safety profile, requires further study to assess its use in preventing peri-operative bleeding.

Gastrointestinal haemorrhage

Bleeding from the gastrointestinal tract can be catastrophic even in those without a pre-existing coagulopathy. Table 4 summarizes three such cases where rFVIIa was used with good effect and no complications directly attributable to rFVIIa.^{87,88} The administration of rFVIIa to patient 3 reduced but did not stop bleeding. However, the patient became sufficiently haemodynamically stable to allow for angiographic intervention after which further haemorrhage did not occur.

Preterm neonates with bleeding complications

Premature neonates are yet another group of patients in whom bleeding complications are a major cause of morbidity and mortality. They often have a prolonged PT and low levels of coagulation factors.⁸⁹ rFVIIa was given to preterm neonates with a INR of greater than 2. There was a reduction in the INR which was dose-dependent and which was sig-

nificantly better than that achieved with FFP treatment. The trial was small (16 patients in total) and not designed to look at the clinical effect of rFVIIa.⁸⁹ However, there were significant bleeding episodes amongst the babies despite treatment with rFVIIa. Further evaluation is required.

Haemorrhage within the central nervous system

rFVIIa has been shown to be safe and efficacious in the treatment of bleeds involving the central nervous system (CNS) in a small group of haemophilic patients with inhibitors.⁹⁰

This use has extended to non-haemophilic patients undergoing cerebral events. Tobias⁹¹ reported the successful use of rFVIIa after antifibrinolytics and fresh frozen plasma failed to treat bleeding complications in two children undergoing posterior spinal fusion.

Stroke is a major cause of disability and death. Intracerebral haemorrhage accounts for 15% of strokes. It is less treatable than ischaemic stroke and causes a higher morbidity and disability rate. Data suggest that early haematoma growth is the principal cause of early neurological deterioration. Studies indicate that early haematoma growth occurs in 13–38% of patients scanned within 3 h of onset of intracranial haemorrhage. Working on the hypothesis that the use of 'ultra-early' haemostatic therapy may limit haematoma growth, a randomized double-blind placebo-controlled dose ranging trial of rFVIIa is in progress.⁹²

Safety considerations

The mechanism of rFVIIa in initiating haemostasis has led to concerns that as well as acting locally at the site of vessel injury, more widespread coagulation could be precipitated if tissue factor is in contact with plasma, e.g., when tissue factor is upregulated on the surface of circulating monocytes in the setting of endotoxin administration and in gram negative septicaemia resulting in a disseminated intravascular coagulation.

Tissue factor is expressed within the lipid core of atherosclerotic plaques⁹³ and is exposed at sites of plaque fissure. Administration of rFVIIa to those with atherosclerosis could hypothetically generate an acute thrombus if tissue factor is exposed. However, it is not clear from our current understanding of atherosclerosis, how often tissue factor is exposed to blood. It may become exposed at the time of plaque rupture, but how often do plaques

rupture in individuals? This is currently unknown. It is known, however, that administration of rFVIIa caused an increase in infarct size in an animal model of myocardial infarction.⁹⁴ Certainly inhibitors of the FVIIa/TF complex reduce infarct size and prevent carotid re-occlusion post-thrombolysis.⁹⁵ These concerns have resulted in careful use of rFVIIa in the setting of cardiac surgery and in patients with risk factors for atherosclerotic disease.

In practice so far, however, studies establishing the role of rFVIIa in the treatment of Haemophilia patients showed it was well tolerated.^{96,97,98} More than 160,000 doses were given for licensed indications to August 2000. During this period, a total of 26 serious adverse events were reported to the manufacturers. In total, six cases of myocardial infarction and four cerebrovascular events occurred.⁹⁹ The majority of these patients had either age-related or other risk factors for atherosclerotic disease. This low incidence of events may, however, be falsely reassuring because many patients were very young and thus not expected to have atherosclerosis. Moreover, adult haemophiliacs have a lower prevalence of atherosclerosis than the general population.¹⁰⁰ In the database of adverse events, five patients suffered thrombo-embolic complications after the use of rFVIIa, including one who died as a result of pulmonary embolism. During the clinical trials of the use of rFVIIa in haemophiliacs, there were five patients who developed clinical or laboratory evidence of DIC. Despite this, there have been no cases of clinical DIC reported so far with its licensed use. Indeed, rFVIIa has been used successfully to treat bleeding complications associated with a picture of DIC. In the case of a pregnant woman presenting with hepatic impairment, renal failure, elevated d-dimers and prolonged PT, APTT (27 and >60 s, respectively), a caesarian section was performed which was complicated by 4 days of severe post-operative bleeding.¹⁰¹ This continued despite intensive blood component support and surgical procedures including a hysterectomy and repeated explorations and packing. She was given 90 mcg/kg rFVIIa every 3 h with a rapid improvement in haemoglobin levels and shortening of the PT. Resolution of biochemical and indices of coagulation followed.

In summary, care is being exercised in the wider application of rFVIIa. Concerns about generalized activation of coagulation and possible thrombosis in pre-disposed patients remain. For example, a trial of rFVIIa in prevention of re-bleeding in subarachnoid haemorrhage was suspended after a patient developed a cerebral artery thrombosis contralateral to the side of the aneurysm.¹⁰² The use of rFVIIa in patients with risk factors for DIC,

thromboembolic or atherosclerotic disease should be being avoided unless the patient is being entered into large randomized controlled trials to demonstrate safety and efficacy.

Conclusions

The appropriate management of bleeding in patients is to diagnose the specific defects underlying the bleeding and treat the cause and use appropriate blood products to restore blood volume and haemostasis. Bleeding in a patient that does not respond to conventional blood component use, and where surgery is hampered by widespread ooze, demands improved management options. Management may be improved by better use of blood components, better use of laboratory haemostatic monitoring, antifibrinolytics and surgical re-exploration.¹⁰³ However, at times bleeding defies even these options and in this setting rFVIIa is often considered, although efficacy and safety studies are far from complete.

This paper has reviewed the wide number of bleeding indications in which rFVIIa has been investigated. The need for systematic, standardised reporting of cases has been recognized. Encouragingly, many new trials are planned and underway.⁹² If safety and efficacy of rVIIa become established in the context of randomized, controlled and blinded trials, then it has an exciting future.

Practice points

- If a patient has massive bleeding, ensure that appropriate blood component therapy has been used, before considering the use of rVIIa.
- Do not forget to consider an antifibrinolytic agent in the management of uncontrolled bleeding.
- The use of the TEG may help resolve the pathogenesis.
- If rVIIa use is considered, please encourage clinical staff to use it within the context of a clinical trial.

Research directions

- Randomized controlled studies of the efficacy and safety of rVIIa in bleeding patients in the many different settings described in this paper are urgently required.
- A laboratory means of assessing the clinical efficacy of rVIIa is required.

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