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Ongoing NovoSeven® trials

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Abstract Recombinant activated factor VII (rFVIIa, 'NovoSeven®') was initially developed for the treatment of bleeding in patients with haemophilia and inhibitors, and is currently licensed in most countries worldwide. The mechanism of action suggests that its enhancing effects in haemostasis are limited to the site of injury and that systemic activation of the coagulation cascade does not occur. These properties, together with anecdotal reports of its beneficial effects in different patient populations with severe bleeds, suggest that rFVIIa may be valuable as a general haemostatic agent. In case reports, rFVIIa has been reported to

reduce bleeding in patients with liver disease, thrombocytopenia or thrombocytopathia, trauma, those undergoing radical prostatectomy or receiving oral anticoagulant therapy. A number of clinical trials have recently been initiated to collect data on the safety and efficacy of rFVIIa in these patient groups. The beneficial effects of rFVIIa occurring in these studies will support the potential use of rFVIIa as a universal haemostatic agent.

Keywords Recombinant activated factor VII (rFVIIa) · NovoSeven · Haemostasis · Bleeding

Introduction

Recombinant activated factor VII (rFVIIa, 'NovoSeven®') is licensed in many countries worldwide for the treatment of spontaneous and surgical (excluding the USA) bleeding in patients with haemophilia and inhibitors. It is also approved in Europe and other areas for use in bleeding episodes in patients with acquired haemophilia. Evidence from its extensive use in the haemophilic population demonstrates that rFVIIa enhances haemostasis at the site of injury, apparently without systemic activation of the coagulation cascade. At pharmacological doses, rFVIIa restores haemostasis by enhancing thrombin generation on the activated platelet surface; consequently, patients with disorders in which thrombin generation is impaired and bleeding is a problem may benefit from its use. Indeed, anecdotal reports and data from small studies suggest the potential of rFVIIa as a valuable general haemostatic agent for bleeding episodes beyond its

current indications of haemophilia with congenital or acquired inhibitors [1].

Recombinant activated factor VII and haemophilia with inhibitors

Inhibitors are alloantibodies that may be generated against coagulation factors VIII (FVIII) or IX (FIX) in haemophilia patients who have received factor replacement therapy (plasma, cryoprecipitate or FVIII/FIX concentrates). These immunoglobulins partially or completely neutralise the clotting activity of their respective factor concentrates, rendering subsequent replacement therapy partially or completely ineffective [2]. In vitro observations in animal [3, 4] and cell models [5, 6, 7] have demonstrated the potential for rFVIIa use and its mechanism of action in patients with haemophilia and inhibitors. Moreover, the therapeutic efficacy and clinical

Fig. 1 Thrombotic adverse events reported in haemophilia patients receiving recombinant activated factor VII (rFVIIa) between 1996 and October 2001. During this period more than 480,000 standard doses of rFVIIa were administered. The time scale indicates days after initiation of treatment (day 0). rFVIIa was administered as a single intravenous dose or as repeated bolus injections (denoted by *arrows*); in patient 2, rFVIIa was administered as a continuous infusion. (*AH* acquired haemophilia, *AMI* acute myocardial infarction, *CVT* cerebrovascular thrombosis, *DIC* disseminated intravascular coagulation, *IH* inherited haemophilia, *PE* pulmonary embolism, *VT* venous thromboembolism)

Dose (µg/kg)	Age (years)		0	1	2	3	4	5	6	7	65 days
30	57	IH									DIC
40	70	AH					AMI				
78	71	AH		AMI							
80	38	IH									CVT
84	26	IH		AMI							
85	77	AH									AMI
90	70	AH									DIC
90	91	AH									CVT
90	50	AH									CVT
90	50	AH									PE
90	27	IH									VT
90	39	IH									VT
100	79	IH		AMI							
100	72	IH		AMI							
120	16	I									VT
?	20	?									VT
?	57	AH									VT

cal safety of rFVIIa have been investigated since 1988 in a number of clinical trials, including the Compassionate Use Study [8], the Emergency Use Study [9], the Home Treatment Study [10] and the Surgery Study [11].

Clinical data from these and other studies demonstrated rFVIIa to be effective in controlling bleeds in various settings, including haemophilic patients with serious bleeding refractory to other treatments [12], joint or muscle bleeds [12, 13], in those undergoing surgical procedures [8, 11, 14, 15, 16] and in the home-treatment setting [10]. Since its approval in 1996 and until October 2001, more than approximately 480,000 standard doses of rFVIIa have been administered. During this period, 17 thrombotic spontaneous adverse events were reported in haemophilia patients (acquired and inherited) (Fig. 1). There was no evidence of a dose relationship and more than one-third of patients experiencing thrombotic adverse events were aged over 70 years. Moreover, an alternative aetiology for thrombosis was identified in all cases. Accordingly, rFVIIa was considered to have a strong safety platform from which to proceed with further clinical development in other patient groups.

Investigational uses of recombinant activated factor VII

Preclinical evidence indicates that rFVIIa increases thrombin generation on the activated platelet surface and improves an impaired initial haemostasis [17, 18]. Accordingly, rFVIIa has the therapeutic potential to establish haemostasis in bleeding disorders associated with liver disease or oral anticoagulant treatment [in which endogenous factor VII (FVII) levels may be low], in

addition to conditions characterised by reduced platelet surface thrombin generation, such as haemophilia, platelet disorders, intracerebral haemorrhage and diffuse bleeding triggered by surgery or trauma.

The following sections summarise the clinical evidence for the use of rFVIIa in these conditions, which has led to the design and initiation of a number of clinical trials (Table 1).

Platelet disorders

Conditions involving decreased platelet numbers are associated with reduced thrombin formation [19] and current therapies that act locally to stop such thrombocytopenic bleeding are usually combined with platelet transfusion. However, the development of platelet allo-antibodies occurs commonly, and subsequent platelet transfusions become ineffective in controlling bleeding.

In vitro evidence indicates that rFVIIa 50–500 nM increases initial thrombin generation and shortens the lag phase of platelet activation in a thrombocytopenic cell model [18]. Data from a phase I/II study in 74 thrombocytopenic patients and a single case study in a patient refractory to platelet transfusion (Table 2) indicated evidence for the use of rFVIIa in promoting haemostasis in individuals with low platelet counts [20].

Allogenic stem cell transplantation (ASCT) is an effective treatment for many malignant or benign disorders of the bone marrow. However, prior to this procedure, the patients' bone marrow cells (both diseased and healthy) must be destroyed by induction chemotherapy or radiotherapy, rendering the patient thrombocytopenic until ASCT with new progenitor cells occurs. During this interim period, pa-

Table 1 Summary of ongoing randomised, multicentre clinical trials to investigate the efficacy and safety of recombinant activated factor VII (*rFVIIa*) for bleeding in non-haemophilic patient populations. All studies were double-blind and placebo-controlled, with the exception of the oral anticoagulant toxicity study in which

standard therapy was used as the comparator (*SOT* start of treatment, *PRBC* packed red blood cells, *ICH* intracerebral haemorrhage, *CT* computed tomography, *GI* gastrointestinal, *RBC* red blood cells, *FFP* fresh frozen plasma, *PCC* prothrombin complex concentrates)

Study population	<i>n</i>	Treatment	Primary efficacy end point
Thrombocytopenia			
Patients with moderate-to-severe bleeds after allogeneic stem cell transplantation	100	Standard therapy + rFVIIa 40, 80 or 160 µg/kg or placebo at specific time points	Change in bleeding score from baseline to 38 h after SOT
Trauma			
Patients with severe blunt and/or penetrating trauma	280	Standard therapy + 3 doses of rFVIIa	No. of PRBC units (allogeneic/autologous) transfused within 48 h of SOT
Intracerebral haemorrhage			
Patients with acute ICH	80	rFVIIa 10, 20, 40, 80, or 120 µg/kg or placebo	Change in ICH volume as measured by CT from baseline to 24h CT scan
Liver disease			
Cirrhotic patients with acute upper GI bleeding and signs of portal hypertension	240	rFVIIa 100 µg/kg or placebo at specific time points	Composite 5-day end point: control of GI bleeding, prevention of rebleeding, mortality
Cirrhotic patients undergoing partial hepatectomy	240	rFVIIa 50 or 100 µg/kg or placebo at specific time points	RBC transfusion requirements during partial hepatectomy and 48 h postoperative period
Non-cirrhotic patients undergoing partial hepatectomy	180	Single dose of rFVIIa 20 or 80 µg/kg or placebo	RBC transfusion requirements during partial hepatectomy and 48 h postoperative period
Patients undergoing liver transplantation	180	rFVIIa 60 or 120 µg/kg or placebo at specific time points	RBC transfusion requirements during surgery and 24 h postoperative period
Oral anticoagulant toxicity			
Patients with severe bleeds receiving vitamin K antagonist treatment	210	rFVIIa 40 or 80 µg/kg at specific time points	Effect on bleeding 6 h after treatment initiation (stopped, decreased, unchanged, worsened)

Table 2 Summary of the efficacy of recombinant activated factor VII (*rFVIIa*) in patients with thrombocytopenia (*AML* acute myeloid leukaemia)

Reference	<i>n</i>	Clinical presentation	rFVIIa (µg/kg)	No. of doses	Post-rFVIIa outcome
Kristensen et al. 1996 [20]	74	Thrombocytopenia	50, 100	≥1	Shortening of bleeding time in 52% of patients
	8	Thrombocytopenia with overt bleeding	50, 100	1–2	Overt bleeding stopped in six patients and slowed in two patients
Vidarsson and Onundarson 2000 [51]	1	Thrombocytopenia (platelet count <150×10 ⁹ /L) secondary to AML refractory to platelet transfusion	100	11	Haemostasis achieved, peri-orbital haematomas resolved. Platelet count remained low due to persistent leukaemia; the patient died after unsuccessful re-induction chemotherapy

tients have a high bleeding risk. Accordingly, a randomised, double-blind, placebo-controlled study is currently being undertaken to evaluate the efficacy and safety of rFVIIa administered to thrombocytopenic patients with moderate-to-severe bleeding after stem cell transplantation (Table 1).

Trauma

Patients who experience severe trauma may develop uncontrolled bleeding requiring transfusion [21], and acute trauma may cause alterations in coagulation and fibrinol-

Table 3 Summary of the efficacy of recombinant activated factor VII (rFVIIa) after failure of conventional haemostatic measures in patients experiencing blunt or penetrating trauma (PBRC packed red blood cells)

Reference	<i>n</i>	Clinical presentation	rFVIIa (µg/kg)	No. of doses	Post-rFVIIa outcome
Kenet et al. 1999 [25]	1	Intra-abdominal gunshot wound. Bleeding rate 300 mL/min	60	2	Decrease in bleeding rate to 10–15 mL/min within 10 min of administration. Slow oozing stopped after second dose. No further blood loss
Martinowitz et al. 2001 [26]	7	Massively bleeding, multi-transfused, coagulopathic trauma patients	120–212	1–3	Cessation of diffuse bleeding within 5–15 min. Significant reduction in PRBC requirements. Three patients died: one during surgery, two at 4 weeks post-operation
O'Neill et al. 2002 [27]	1	Massive haemorrhage from grade III liver injury after multiple stab wounds	90	1	Almost immediate after the bleeding cessation and correction of coagulopathy. No further episodes of bleeding. The patient died from multiple organ failure secondary to sepsis 5 weeks injury

ysis [22]. Massive bleeding in trauma cases may present as a combination of bleeding from vessels needing surgical treatment (surgical bleeding) and diffuse uncontrolled bleeding from small vessels (coagulopathic bleeding). Coagulopathy in trauma is multifactorial: excessive fibrinolysis, dilutional coagulopathy caused by excessive fluid treatment and blood loss, massive transfusion syndrome and hypothermia [23]. Observations from clinical case histories and preliminary studies show that rFVIIa successfully prevents or reduces bleeding in haemophilic patients undergoing elective surgery [11] and in individuals with normal coagulation undergoing transabdominal prostatectomy [24]. In addition, a preclinical study of liver injury in pigs showed rFVIIa to be an effective treatment for reducing blood loss in trauma [23].

A small number of clinical case reports on the use of rFVIIa after trauma and bleeding have been published and are summarised in Table 3 [25, 26, 27]. These case histories involve eight patients and indicate that rFVIIa may be effective in managing trauma-associated bleeding. rFVIIa has been well tolerated in this patient group. A large study is currently underway to investigate the use of rFVIIa in stopping severe bleeding in patients who have experienced trauma (Table 1).

Intracerebral haemorrhage

Neurological deterioration occurring after intracerebral haemorrhage (ICH) is strongly associated with early hae-

matoma growth and haematoma volume is a powerful predictor of 30-day mortality [28, 29, 30, 31, 32, 33]. As haematoma growth is a dynamic process in acute ICH, intervention with ultra-early haemostatic therapy could minimise, and possibly even prevent, early growth. The rapid action of rFVIIa (half-life 2.5 h) at the local bleeding site, coupled with its apparent low risk of systemic adverse events, has highlighted this agent as a potentially valuable haemostatic treatment during the high-risk stage of ICH.

Although no studies investigating the use of rFVIIa in ICH have been published, a clinical study is currently underway to evaluate its safety and efficacy in reducing the frequency of early haematoma growth in patients with acute ICH (Table 1).

Liver disease

The coagulopathy of liver disease is a major contributor to its associated high morbidity and mortality in the USA and Europe [34]. Liver disease can impair haemostasis by a number of mechanisms, such as disrupting functional clotting factor synthesis, increasing fibrinolysis, prolonging prothrombin time (PT) or causing thrombocytopenia [35]. The progressive loss of liver parenchymal cells associated with cirrhosis results in a decreased synthesis of the vitamin K-dependent coagulation factors (FII, FVII, FIX, FX) and proteins C and S. FVII is the most sensitive to this liver cirrhosis due to

Table 4 Summary of the efficacy of recombinant activated factor VII (*rFVIIa*) in patients with liver disease (*PT* prothrombin time, *OLT* orthotopic liver transplantation, *RBC* red blood cells, *FFP* fresh frozen plasma)

Reference	<i>n</i>	Clinical presentation	rFVIIa (µg/kg)	No. of doses	Post-rFVIIa outcome
Bernstein et al. 1997 [39]	10	Cirrhotic patients with prolonged PT	5, 20, 80	1 at each dose level	Dose-dependent period of PT normalisation
Jeffers et al. 2002 [40]	65	Patients with cirrhosis undergoing laparoscopic liver biopsy	5–120	1–2	Dose-dependent reduction of prolonged PT
Papatheodoridis et al. 1999 [41]	1	Solitary hepatocellular carcinoma and underlying hepatitis	80	2	Improvements in PT and platelet function within 10 min of a single dose, effects maintained for 4–8 h. No subsequent bleeding or complications
Hendriks et al. 2001 [42]	6	Patients undergoing OLT	80	1	Significant 67% and 88% reductions in RBC and FFP requirements, respectively, compared with matched controls
Chuansumrit et al. 2001 [43]	5	Paediatric patients (aged 2 months–14 years) with massive haematemesis or undergoing liver biopsy. Bleeding refractory to FFP and RBC transfusion	40	1–8	Haemostasis achieved, allowing therapeutic or diagnostic surgical procedures to be performed

its low half-life [36]. Bleeding risks in patients with liver disease include gastrointestinal bleeds, bleeding during routine procedures such as biopsy, or during major surgery such as liver transplantation [37]. Partial hepatectomy is an important treatment modality for primary and secondary liver tumours but, in cirrhotic patients, it is associated with significant intraoperative blood loss, probably due to liver-dependent coagulopathy, and transfusion requirements are high. During other major surgical procedures, such as orthotopic liver transplantation, bleeding can be a considerable problem and excess blood loss is associated with increased morbidity, mortality and intensive care stay [38]. Blood transfusions are required, even in uncomplicated patients, as surgical bleeding is compounded by the abnormal coagulation state frequently associated with the dysfunction of a diseased liver.

As patients with liver disease have compromised haemostasis, notably an impaired thrombin generation system, rFVIIa was proposed as a potential agent for managing bleeding episodes in these patients to compensate for defective coagulation parameters. Clinical data from a limited number of case histories and small trials ($n=87$ patients) indicate that rFVIIa might have the potential to be an effective haemostatic measure in patients with liver disease and bleeding (Table 4) [39, 40, 41, 42, 43]. A number of studies are currently investigating the use of rFVIIa in patients with liver disease. These include liver transplantation, acute upper gastrointestinal bleeding in patients with cirrhosis and signs of portal hy-

pertension, and patients with or without liver cirrhosis undergoing partial hepatectomy (Table 1).

Oral anticoagulant therapy and bleeding complications

Patients receiving long-term anticoagulant therapy with oral vitamin K antagonists, such as warfarin and acenocoumarol, commonly experience mild-to-moderate bleeding and 10–12% have been reported to experience major bleeds, especially when therapy continues over an extended period [44, 45]. Existing therapy for acute reversal of oral anticoagulant-induced toxicity consists of administration of fresh frozen plasma or prothrombin complex concentrates. Although many coagulation factors are susceptible to oral anticoagulant therapy, FVII levels are those most markedly affected, reducing to approximately 10% of normal values [46, 47].

Evidence for the use of rFVIIa is available from a small number of reports in patients with spontaneous bleeds and critically prolonged international normalised ratios (INRs), together with a single study involving 28 healthy volunteers with experimentally prolonged INRs (Table 5) [48, 49, 50]. These reports indicate that rFVIIa can correct the INR and, as such, may be a useful agent for reversing the effects of over-anticoagulation with vitamin K antagonist therapies. However, further data from large patient populations are needed to establish the efficacy and safety of this therapeutic approach. To this end, a study is ongoing to compare the efficacy and

Table 5 Summary of the efficacy of recombinant activated factor VII (rFVIIa) in individuals receiving oral anticoagulant treatment (*hv* healthy volunteers, *INR* international normalised ratio, *PT* prothrombin time)

Reference	<i>n</i>	Clinical presentation	rFVIIa (µg/kg)	No. of doses	Post-rFVIIa outcome
Erhardtson et al. 1998 [48]	28 hv	Acenocoumarol-induced INR >2.0	5–320	1	Normalisation of INR and PT. Dose-dependent time period of INR normalisation
Berntorp et al. 2000 [49]	1	Profuse bleeding from nose and throat, INR 2.9	80	2	INR reduced to 1.4 within 15 min
Deveras and Kessler 2000 [50]	7	Critically prolonged INR (3.2–13.9)	20–90	1	Considerable reduction in INR and PT

safety of rFVIIa with that of standard treatment in patients experiencing severe bleeds during treatment with vitamin K antagonist therapy (Table 1).

Summary

In vitro and clinical data show that rFVIIa has a beneficial effect by increasing thrombin formation and, thereby, the potential to control bleeding. There are extensive data to substantiate that rFVIIa is safe and effective for the treatment of bleeding in patients with haemophilia and inhibitors. Early efficacy and safety data in a small number of individuals have been obtained for

investigational uses, including bleeding associated with thrombocytopenia, trauma, liver disease and oral anticoagulant toxicity. However, to assess the true potential of rFVIIa in these therapy areas, large randomised controlled trials must be performed. Currently, several clinical studies are being conducted to investigate the use of rFVIIa in these patient groups. These trials will specifically focus on spontaneous or surgical bleeding in patients with liver disease, patients with bleeding due to thrombocytopenia, patients with intracerebral haemorrhage and individuals who have experienced trauma. Positive outcomes from these studies will provide strong support for the use of rFVIIa as a universal haemostatic agent.

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