



Brief Clinical Observation

Prophylactic and therapeutic use of recombinant activated factor VII in patients with cirrhosis and coagulation impairmentE. Tsochatzis^a, G.V. Papatheodoridis^{a,*}, I. Elefsiniotis^b, S. Thanelas^b,
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Abstract

Patients with cirrhosis and impaired coagulation often pose major therapeutic problems during bleeding episodes or invasive procedures. Recombinant activated factor VII (rFVIIa), which has been licensed for the treatment of haemophilia patients with factor VIII or IX inhibitors, has been occasionally used in cirrhotic patients. We present five patients with cirrhosis and coagulopathy who received 1–4 recombinant activated factor VII infusions either prophylactically in order to safely undergo an invasive procedure or therapeutically in order to control a severe bleeding episode which did not respond to standard supportive care. In particular, recombinant activated factor VII infusions were given in two patients before a percutaneous liver biopsy, in one patient before teeth extraction and in two patients with haemoperitoneum after an invasive procedure. Infusions of recombinant activated factor VII achieved rapid correction of prothrombin time in all cases allowing the safe performance of invasive procedures or resulting in efficient control of the bleeding episode. In conclusion, recombinant activated factor VII seems to be a rather promising agent for the prevention or treatment of complications of haemostasis impairment in cirrhotic patients. However, its exact role in this setting needs to be evaluated within well-designed, controlled clinical trials.

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Impaired haemostasis is invariably present in patients with advanced liver disease due to impaired coagulation expressed by prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT) and/or low platelet count [1,2]. Although cirrhotic patients do not frequently experience spontaneous bleeding despite impaired haemostasis, they certainly are at increased risk of severe bleeding during any bleeding episode or after common invasive procedures [3]. Management of impaired haemostasis in cirrhotic patients has not substantially changed over the last decades and is based on fresh frozen plasma (FFP) and/or platelets

transfusions, while parenteral admission of Vitamin K may have a beneficial effect only in cases with prolonged cholestasis. However, it is often difficult to correct haemostasis and particularly coagulopathy in cirrhosis because the transfusion volume required may be too large [4]. Moreover, since both FFP and platelets are human blood products, there is always a risk of transmitting infection of unknown or undetectable agents.

Impaired coagulation in cirrhosis develops due to deficiencies of the Vitamin K-dependent coagulation factors. Factor VII has the shortest half-life and its levels have been suggested as a good prognostic marker for the severity of liver disease, since they decrease before the levels of other coagulation factors [1,2]. The recent development of recombinant activated factor VII (rFVIIa), which was initially used for the treatment of patients with haemophilia A and B, particularly

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Table 1
Main characteristics of five patients with decompensated cirrhosis treated with rFVIIa

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	55	73	46	64	40
Gender	Female	Male	Male	Female	Male
Weight (kg)	75	70	75	80	80
Cause of cirrhosis	Alcohol abuse	Alcohol abuse	HCV	Alcohol abuse	Alcohol abuse
Child class	C	C	C	B	C
Hb (g/dL)	9	12.9	10.6	6.7	7.3
WBC ($\times 10^9/L$)	13.1	7.3	8.9	11.7	8.2
PLT ($\times 10^9/L$)	311	118	53	162	40–55
PT (s)	35	28	29	21	33
INR	3.1	2.3	2.3	1.9	3.2
aPTT (s)	74	53	82	43	94
Fibrinogen (mg/dL)	266	650	97	337	134
Albumin (g/dL)	3.3	2.3	3.0	3.3	2.4
Bilirubin (mg/dL)	17	9	9	7	14

Hb: haemoglobin; WBC: white blood count; PLT: platelet count; PT: prothrombin time (normal range: 12–14 s); INR: international normalised ratio (normal range: 1.0–1.2); aPTT: activated partial thromboplastin time; HCV: hepatitis C virus; and HBV: hepatitis B virus.

Table 2
Dosage of rFVIIa infusions given prophylactically or therapeutically in five patients with decompensated cirrhosis

	Case 1	Case 2	Case 3	Case 4	Case 5
rFVIIa dose ($\mu\text{g/kg}$)	48	34	80	60, 47.5	45
Number of doses	2	1	4	1, 2	4
Dosing interval (h)	24	–	8, 16, 8	4	8, 24, 24

those with inhibitors against factors VIII and IX, respectively, was suggested as a promising therapeutic option for the hypocoagulable state associated with liver disease [5]. In particular, administration of a single dose of rFVIIa was initially shown to correct the prolonged PT and aPTT in non-bleeding cirrhotic patients in a dose dependent manner [6], while beneficial effects of rFVIIa infusions have been reported in cirrhotic patients with severe bleeding episodes or undergoing invasive procedures [7–11]. We present five patients with cirrhosis and coagulation impairment who received infusions of rFVIIa (NovoSeven, NovoNordisk, Copenhagen, Denmark) used either prophylactically before invasive procedures or as rescue therapy in order to control major bleeding episodes not responding to usual therapeutic intervention. The main characteristics and laboratory tests before the rFVIIa infusions and the dosages of rFVIIa infusions in these five patients appear in Tables 1 and 2, respectively.

1. Case 1

A 55-year-old woman was admitted to our hospital due to decompensated cirrhosis of unknown aetiology. Her medical history was unremarkable and she denied alcohol or any drug use, while a full work-up was negative for all known causes of chronic liver disease. On presentation, international normalised ratio (INR) was 1.4 but her coagulation status deteriorated rapidly with INR increasing to 3.1 despite intravenous injections of Vitamin K and transfusions of FFP. Thus, although a liver biopsy was considered to be a method that might help in the aetiological diagnosis of her liver disease, it

was impossible to be performed percutaneously. Since there was no possibility for transjugular liver biopsies in our hospital, the use of rFVIIa infusions was decided in an attempt to improve coagulation status and thus safely perform a percutaneous liver biopsy after having the patient's informed consent.

Twelve hours after the last FFP transfusion and 1 h before the liver biopsy, 3.6 mg (48 $\mu\text{g/kg}$) of rFVIIa were given as a slow intravenous injection. Half an hour later, her INR was 1.0 and a percutaneous liver biopsy was performed. INR increased to 1.5 s at 10 h and to 3.5 at 24 h after the infusion. A second rFVIIa infusion of 3.6 mg was given at 24 h achieving similar changes of coagulation tests. No clinical or laboratory adverse event was observed. Histological examination revealed findings consistent with alcoholic hepatitis.

2. Case 2

A 73-year-old retired farmer with a 2-year history of decompensated alcoholic cirrhosis presented with progressively increasing hepatocellular and cholestatic enzymes levels over the last 3 months. Computed tomography (CT) scan showed a focal lesion with a diameter of 4 cm in the left hepatic lobe and signs of possible thrombosis of the portal vein, while alpha-fetoprotein was normal.

A percutaneous CT guided liver biopsy was decided to be mandatory for diagnosis, but his INR was 2.3 despite FFP transfusions. Thus, the use of rFVIIa infusions was decided in order to perform the liver biopsy safely and the patient's informed consent was obtained. An intravenous infusion

of 2.4 mg of rFVII (34 $\mu\text{g}/\text{kg}$) was administered, INR normalised soon and a CT guided percutaneous liver biopsy was performed 1 h later. Twenty-four hours after rFVIIa infusion, INR was 2.2, but rFVIIa was not administered again, since the patient was asymptomatic without any clinical or laboratory adverse event or any radiological sign of bleeding. Histological examination of the specimen revealed hepatocellular carcinoma.

3. Case 3

A 46-year-old man with decompensated hepatitis C virus (HCV) cirrhosis was admitted for performing dental extraction as preparation for undergoing orthotopic liver transplantation (OLT). One week before, he had undergone one tooth extraction as outpatient, which had been complicated by prolonged haemorrhage and had resulted in emergent admission to another hospital. He had been treated with FFP and red pack cells transfusions and the bleeding episode had been controlled after 48 h. Transfusions of FFP were given without any significant effect on coagulation tests and therefore the use of rFVIIa infusions was decided. However, FFP transfusions continued because of his low fibrinogen levels (five FFP units before each rFVIIa infusion) and tranexamic acid was decided to be administered after rFVIIa infusions.

Fifteen minutes after the first rFVIIa infusion of 6 mg (80 $\mu\text{g}/\text{kg}$), INR was 1.4 and he underwent extraction of three teeth. A second rFVIIa infusion of 6 mg was repeated 8 h after the first one. No major bleeding was observed from the extraction sites during the next 24 h, while INR increased to 2.1 at 24 h after the first rFVIIa infusion. The next day, two additional rFVIIa infusions of 6 mg were administered with an 8-h interval, while three more teeth were uneventfully extracted. Six hours after the last rFVIIa infusion, the patient was treated with tranexamic acid at a dose of 1 g every 8 h for 4 days. Again, no major bleeding was observed from the extraction sites over the next 48 h.

4. Case 4

A 64-year-old woman presented with 1-month history of fatigue and increasing jaundice due to alcoholic cirrhosis. A liver biopsy was decided in order to confirm or exclude a superimposed acute alcoholic hepatitis. Her INR was corrected by transfusions of four FFP units and a percutaneous liver biopsy was performed, which showed alcoholic cirrhosis and alcoholic hepatitis. However, 48 h later, when her INR raised again to 1.9, the patient developed haemoperitoneum, which did not subside despite transfusions FFP and packed red cells over the next 24 h.

As the bleeding continued, a total of three rFVIIa infusions were administered in 4-h intervals. The dose of the first rFVIIa infusion was 4.8 mg (60 $\mu\text{g}/\text{kg}$) and of the next two infusions 3.6 mg (47.5 $\mu\text{g}/\text{kg}$). INR normalised within the

first hour after the first rFVIIa infusion and remained within normal range for 24 h returning to baseline levels (1.9) at 24 h after the third rFVIIa infusion. Based on the patient's clinical signs, Hb levels and the quantity of ascitic fluid, the bleeding episode was successfully treated without signs of active blood loss over the next days.

5. Case 5

A 40-year-old man with alcoholic cirrhosis was admitted because of worsening jaundice. Physical examination revealed mild encephalopathy and ascites and a diagnostic ascitic fluid paracentesis was tried unsuccessfully. Over the next 72 h, the patient developed clinical and laboratory findings of intraperitoneal haemorrhage, which persisted over the next 48 h despite transfusions of several units of FFP and red pack cells. Thus, use of rFVIIa was decided and he received four rFVIIa infusions of 3.6 mg (45 $\mu\text{g}/\text{kg}$) at 8-h intervals for the first two and 24-h intervals for the last two doses. INR was 1.8 before the second and 1.4 at 8 h after the second rFVIIa infusion, while it prolonged again to 2.2 just before the third and improved to 1.6 at 8 h after the third rFVIIa infusion. All signs of active bleeding subsided after the second rFVIIa infusion without any evidence of bleeding recurrence over the next 4 days.

6. Discussion

We described five patients with cirrhosis and severe coagulation impairment who received infusions of rFVIIa either prophylactically or therapeutically. All our patients had advanced liver disease with four being classified into Child class C and one into Child class B cirrhosis (Table 1). Moreover, three patients had low PLT of around $50 \times 10^9/\text{L}$, which is a recently suggested cut-off PLT level in order to get better results with rFVIIa infusions [12]. Our study was not a prospective trial, but it provides information on several cases with decompensated cirrhosis, most of which have not been adequately evaluated yet.

Up to now, there has been only one controlled trial addressing the prophylactic use of rFVIIa infusions in cirrhotic patients [13], while all other relevant data come from case reports [7,11]. We successfully administered this agent to two patients before a percutaneous liver biopsy and to one patient before dental extractions. It should be noted that FFP transfusions had been ineffectively tried to correct PT before the use of rFVIIa in all three cases. Transjugular liver biopsy would have been an alternative method for assessing liver histology in one of our patients, but it is not performed in our hospital. Data regarding use of rFVIIa infusions for obtaining liver specimens are limited and mostly come from a study in 71 cirrhotic patients with PT prolongation from 3 to 15 s who underwent laparoscopic liver biopsies [13]. In the latter study, an uneventful biopsy was performed in all 71 patients

pre-treated with any of four different doses of rFVIIa (5, 20, 80, 120 µg/kg), while no significant liver bleeding was observed as assessed by direct observation. In our cases, relatively small doses of rFVIIa were used (34 and 48 µg/kg) and no adverse event was observed.

Data on the use of rFVIIa for performing dental extractions are lacking. Gingiva is a tissue with unpredictable bleeding risk, while it has been suggested that the use of rFVIIa warrants careful consideration in this setting [5]. However, rFVIIa infusions have been reported to treat successfully persistent bleeding following dental extractions in two cirrhotic patients [8]. In our patient, FFP transfusions were also given because of his very low fibrinogen levels, while tranexamic acid was administered after the last rFVIIa infusion. The patient had eventually six teeth extracted within 48 h having received four rFVIIa infusions of 80 µg/kg each.

The therapeutic role of rFVIIa in cirrhosis has been evaluated within trials, which, however, included only patients with variceal bleeding [14,15]. In two of our patients, infusions of rFVIIa at relatively small doses (45–60 µg/kg) were used successfully for the management of uncontrolled bleeding following invasive procedures. Beneficial effects of rFVIIa infusions have also been described in other case reports of cirrhotic patients with persistent bleeding episodes [8–10,16], while treatment failures seem to be few [17]. Thus, the use of rFVIIa as a post-procedure rescue intervention seems to be a very promising therapeutic option in cirrhotic patients and it needs to be assessed in future trials [5].

The optimal dosage of rFVIIa infusions in patients with cirrhosis has not been established. Following the suggestions of our haemophilia experts, relatively low rFVIIa doses ranging from 34 to 60 µg/kg were used in all but one of our patients (80 µg/kg) given in 1–4 infusions at intervals ranging from 3 to 24 h (Table 2). Larger doses of rFVIIa (80–120 µg/kg) have usually been used in most case reports and studies to date [7–11,14,15]. In the first study in cirrhotic patients, rFVIIa infusions of 5, 20 and 80 µg/kg were found to normalise PT for 2, 6 and 12 h and maintain PT better than baseline values for at least 12 h [6]. The need for repeated rFVIIa infusions and their optimal intervals remain also unclear. The plasma half-life of an 80 µg/kg rFVIIa infusion in non-bleeding cirrhotic patients is approximately 2.5 h, while PT normalisation after such a dose lasts for about 8 h and plasma FVII levels reach the pre-infusion values at 24 h [18]. The pharmacokinetics of rFVIIa infusions, however, have not been studied in bleeding patients. Thus, further study is needed in order to determine the minimal clinically effective dosage and the best cost-benefit approach of rFVIIa use in patients with cirrhosis.

In conclusion, rFVIIa seems to be a rather promising agent for the prevention or treatment of complications of haemostasis impairment in patients with cirrhosis. However, its wide use in everyday clinical practice in this setting is currently halted by its high cost and the lack of strong evidence. Therefore, the efficacy and cost-effectiveness of prophylactic and therapeutic use of rFVIIa in cirrhotic patients should be evaluated further in clinical trials. Until these issues are

efficiently addressed, it may remain a useful option for cirrhotic patients with hypocoagulable state who develop life threatening bleeding episodes or plan to undergo high-risk invasive procedures.

Conflict of interest statement

None declared.

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