

Recombinant Factor VIIa for Upper Gastrointestinal Bleeding in Patients With Cirrhosis: A Randomized, Double-Blind Trial

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Background & Aims: Upper gastrointestinal bleeding (UGIB) is a severe and frequent complication of cirrhosis. Recombinant coagulation factor VIIa (rFVIIa) has been shown to correct the prolonged prothrombin time in patients with cirrhosis and UGIB. This trial aimed to determine efficacy and safety of rFVIIa in cirrhotic patients with variceal and nonvariceal UGIB. **Methods:** A total of 245 cirrhotic patients (Child-Pugh < 13; Child-Pugh A = 20%, B = 52%, C = 28%) with UGIB (variceal = 66%, nonvariceal = 29%, bleeding source unknown = 5%) were randomized equally to receive 8 doses of 100 µg/kg rFVIIa or placebo in addition to pharmacologic and endoscopic treatment. The primary end point was a composite including: (1) failure to control UGIB within 24 hours after first dose, or (2) failure to prevent rebleeding between 24 hours and day 5, or (3) death within 5 days. **Results:** Baseline characteristics were similar between rFVIIa and placebo groups. rFVIIa showed no advantage over standard treatment in the whole trial population. Exploratory analyses, however, showed that rFVIIa significantly decreased the number of failures on the composite end point ($P = 0.03$) and the 24-hour bleeding control end point ($P = 0.01$) in the subgroup of Child-Pugh B and C variceal bleeders. There were no significant differences between rFVIIa and placebo groups in mortality (5- or 42-day) or incidence of adverse events including thromboembolic events. **Conclusions:** Although no overall effect of rFVIIa was observed, exploratory analyses in Child-Pugh B and C cirrhotic patients indicated that administration of rFVIIa significantly decreased the proportion of patients who failed to control variceal bleeding. Dosing with rFVIIa appeared safe. Further studies are needed to verify these findings.

Upper gastrointestinal bleeding (UGIB) is a severe complication of cirrhosis and portal hypertension, with bleeding from varices accounting for approximately 70% of all UGIB episodes.^{1,2} Mortality associated with variceal bleeding remains high despite improvements in

treatment. Up to 30% of initial bleeding episodes are fatal, and recurrent bleeding episodes further contributing to mortality are common.²⁻⁴

The liver is the principal site of synthesis and clearance of coagulation factors, components of the fibrinolytic system, and naturally occurring anticoagulants. Patients with cirrhosis often have defects in the coagulation system, the most pronounced deficiency being that of factor VII.⁵ Furthermore, in a prospective study, prolonged prothrombin time has been identified as a variable significantly related to 1-year probability of bleeding from esophageal varices.³ In another prospective trial on prophylaxis of bleeding from esophageal varices, low levels of clotting factors II, VII, and X were identified as a significant independent prognostic variable.⁶ UGIB in cirrhotic patients often is massive, and patient management may require large-volume transfusions, which may exacerbate the coagulopathy associated with cirrhosis further. Coagulopathy therefore may be an important predisposing risk factor for failure to control bleeding in cirrhotic patients experiencing UGIB. Patients thus would be likely to benefit from a drug that could correct the coagulopathy and thereby improve hemostasis.

Recombinant activated coagulation factor VII (rFVIIa, NovoSeven; NovoNordisk A/S, Copenhagen, Denmark) currently is approved for the treatment of bleeding episodes in patients with hemophilia with inhibitors, and in the European Union, patients with acquired hemophilia, FVII deficiency, and Glanzmann's thrombasthenia who are refractory to platelets. Case reports and randomized controlled trials, however, indicate the effectiveness of

Abbreviations used in this paper: rFVIIa, recombinant activated coagulation factor VII; UGIB, upper gastrointestinal bleeding.

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rFVIIa in promoting hemostasis in other clinical settings as well.^{7–9} Furthermore, a previous pilot study has shown the ability of rFVIIa to normalize prothrombin time in patients with decompensated cirrhosis and esophageal variceal bleeding.¹⁰ In a study in nonbleeding patients with advanced liver disease, a single dose of 80 $\mu\text{g}/\text{kg}$ rFVIIa normalized the prothrombin time for 12 hours and the half-life of rFVIIa was determined to be approximately 3 hours.¹¹ The effect of rFVIIa at pharmacologic doses is thought to be mediated by increasing the amount of thrombin formed at the site of vessel rupture, thus promoting a tight fibrin structure that is less prone to fibrinolysis.¹²

Standard therapy for acute variceal bleeds focuses on endoscopic treatment (band ligation or sclerotherapy) combined with vasoactive therapy to decrease portal pressure. We hypothesized that treatment with rFVIIa in addition to standard therapy might be of benefit in controlling UGIB in cirrhotic patients. Accordingly, the objective of this trial was to evaluate the efficacy and safety of rFVIIa in cirrhotic patients with acute UGIB.

Materials and Methods

Patients

Patients were enrolled in the trial at 26 hospitals throughout Europe. Patients were required to meet the following inclusion criteria: presence of signs of active acute UGIB suspected to be of variceal origin (i.e., hematemesis or melena within 24 hours of inclusion) requiring hospitalization and volume replacement therapy; presence of cirrhosis, either confirmed histologically or with obvious clinical or endoscopic signs of cirrhosis and portal hypertension; age 18–74 years; scheduled to undergo endoscopy within 12 hours of hospital admission (or within 12 hours of index bleed if already hospitalized); and initiation of trial product administration before first endoscopy and within 6 hours of admission (or within 6 hours of index bleed if already hospitalized). Exclusion criteria included known hypercoagulopathy, acquired FVIII deficiency, or hereditary bleeding disorder; history of pulmonary embolism or deep vein thrombosis within 6 months; history of either portal vein thrombosis, stable/unstable angina pectoris, myocardial infarction, intermittent claudication, or transient ischemic attack/ischemic stroke; signs of cardiac ischemia; concomitant disease with a life expectancy of less than 6 months; tense ascites and obvious jaundice; grade IV encephalopathy; sclerotherapy or band ligation within 2 weeks; previous transjugular intrahepatic portosystemic shunt or orthotopic liver transplantation; known gastrointestinal/respiratory system cancer/hepatocellular carcinoma; planned use of any hemostatic drug other than rFVIIa in the management of the bleeding episode; and known advanced cirrhosis reflected in a known Child–Pugh score¹³ ≥ 12 points at trial entry. The trial protocol was approved by local ethics committees in the partici-

pating countries, and the trial conformed to the Helsinki declaration¹⁴ and guidelines for Good Clinical Practice in clinical trials.

Trial Procedures

During screening, signed informed consent was obtained, inclusion/exclusion criteria were checked, a 12-lead electrocardiogram was obtained, and blood samples were drawn for the determination of liver function as soon as possible before or after treatment allocation. Randomization (computer-generated and stratified by trial center with an equal allocation ratio between rFVIIa and placebo groups and using a concealed block size of 4) was performed immediately after screening procedures through a central interactive voice-response system to administer trial product as early as possible. Patients were randomized to 1 of 2 parallel groups, 8 doses of either 100 $\mu\text{g}/\text{kg}$ rFVIIa or placebo, in addition to standard pharmacologic and endoscopic treatment. The first dose was administered as a slow intravenous injection before first endoscopy and within 6 hours of admission (or within 6 hours of the index bleeding if the patient was already hospitalized). At first endoscopy (to be performed within 12 hours of admission or index bleed) it was assessed whether or not the patient was bleeding actively, and the bleeding source was defined before any procedures were performed to stop the bleeding. Variceal bleeding and active bleeding were defined according to the Baveno criteria.¹⁵ Further doses were administered at 2, 4, 6, 12, 18, 24, and 30 hours after the first dose. Trial product was supplied as sterile, freeze-dried powder in identically appearing single-use vials and was to be reconstituted with sterile water before injection. Common guidelines on endoscopic procedures (sclerotherapy and banding) were adhered to throughout the trial period. Blood transfusions were given to keep hematocrit level between 25%–30%, and vasoactive treatment with either terlipressin, somatostatin, or octreotide was used in accordance with local standard practice. Patients were monitored closely during the 5-day trial period. This included recording signs of active bleeding or rebleeding, emergency and elective procedures, transfusion requirements, adverse events and mortality, as well as monitoring hematocrit and changes in coagulation-related parameters and blood biochemistry. Doppler ultrasound examinations only were performed electively. Mortality, rebleeding, elective procedures, serious adverse events, and hospitalization occurring between days 5–42 were recorded at a follow-up visit 42 days after first trial product administration. An independent data and safety monitoring board was established to provide independent recommendations on safety issues.

To maintain double blinding, treatment allocation was kept in sealed envelopes during the trial, and an equal volume per body weight of trial product was administered to all patients irrespective of treatment allocation.

Outcome Measures and Definitions

The primary objective was to compare the 2 treatment groups with respect to control of acute bleeding, prevention of rebleeding, and mortality over the 5-day trial period. The

primary outcome measure was a composite end point composed of the following 3 end points: (1) failure to control bleeding within 24 hours after first dose of trial product. Failure within 0–6 hours was defined as transfusion of ≥ 4 units of blood (whole blood or red blood cells) together with an inability to achieve an increase in systolic blood pressure by 20 mm Hg or to 70 mm Hg or more. Failure within 6–24 hours was defined by the presence of a new hematemesis together with (a) a decrease in systolic blood pressure ≥ 20 mm Hg and/or (b) a transfusion of ≥ 2 units of blood (whole blood or red blood cells) in addition to the earlier transfusions (given from 0–6 hours) to increase hemoglobin level to ≥ 9 g/dL. In addition to these Baveno II criteria,¹⁶ it was regarded as a failure to control acute UGIB if balloon tamponade was used within 24 hours after first trial product administration. (2) Failure to prevent rebleeding between 24 hours and 5 days defined by the occurrence of new hematemesis and/or new melena together with transfusion of ≥ 2 units of blood (whole blood or red blood cells) in any 24-hour period in which 1 or more of the 3 after hemodynamic criteria were fulfilled: (a) systolic blood pressure < 100 mm Hg, (b) postural change > 20 mm Hg, or (c) pulse rate > 100 beats/min. In addition to these Baveno II criteria,¹⁶ it was regarded as a failure to prevent rebleeding if balloon tamponade was used within 5 days after first trial product administration. (3) Death within 0–5 days after first trial product administration. Failure on the primary composite end point was defined as failure on at least 1 of the 3 end points constituting the composite end point.

Secondary end points included control of acute bleeding and prevention of rebleeding as defined earlier, active bleeding at first endoscopy, 5-day and 6-week mortality, transfusion requirements, number of emergency and elective procedures performed, length of stay in the intensive care unit or hospital, frequency of adverse events including thromboembolic events, changes in coagulation-related parameters (prothrombin time, platelet count, and the levels of fibrinogen, D-dimer, prothrombin fragments 1+2, and thrombin-antithrombin complex), as well as hematology and blood chemistry parameters (hemoglobin, hematocrit, white blood cell count, serum creatinine, calcium, potassium, sodium, bilirubin, serum albumin, alanine transaminase, and alkaline phosphatase).

Statistical Analysis

The trial size was planned to detect a decrease in failure rate on the primary end point from 30% in the placebo group to 15% in the rFVIIa group, with 80% statistical power, and at a significance level of 5%. This translated to a sample size of 240 patients; 120 per treatment arm. Results pertain to patients who were randomized and received trial product. All *P* values are 2 tailed. The type I error was set to 5%. For categoric variables, treatment groups were compared using the Fisher exact test. The analysis was repeated for the population stratified by source of UGIB (variceal/nonvariceal) for all bleeding failure end points. Furthermore, similar analyses were performed post hoc on variceal bleeders stratified by Child–Pugh grade (grades A/B–C) to examine the ability of rFVIIa to

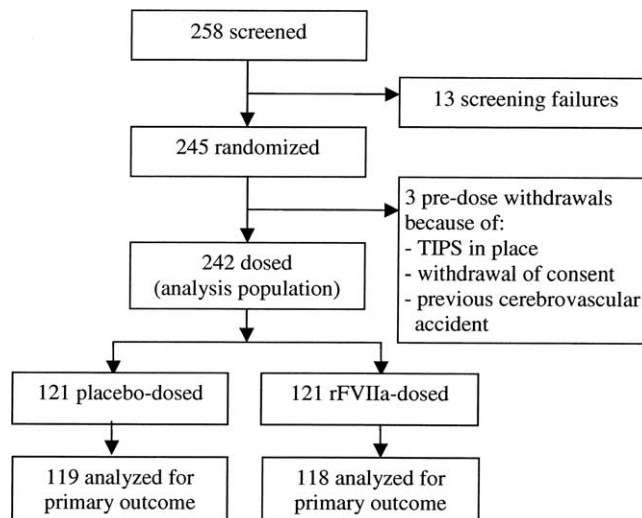


Figure 1. Flow diagram of patient allocation.

compensate for coagulopathies induced by varying degrees of cirrhosis.

Confounding factors were assessed by the logistic regression model for the treatment effect on the primary composite outcome measure and by the Cox regression model for 42-day rebleeding and death rates. The models included the treatment term and variables previously known as prognostic factors for upper gastrointestinal bleeding in cirrhosis¹⁷: cause of cirrhosis, Child–Pugh grade, and source of bleeding.^{18,19} The total number of red blood cell units transfused was compared by using a Wilcoxon–Mann–Whitney test. The number of emergency or elective procedures performed within 5 days and within 42 days, the number of follow-up endoscopies, days in the intensive care unit within 42 days, and days in hospital within 42 days were compared between treatment groups by using exact 2-sample Wilcoxon tests. Adverse events were summarized, and changes in coagulation-related parameters were analyzed by analysis of variance (ANOVA) adjusting for baseline levels or by repeated-measurements ANOVA accounting for intrasubject as well as intersubject variation.

Results

From April 2001 to April 2002, 245 patients were randomized to treatment. Three of these patients, however, were withdrawn before dosing: one because he had a transjugular intrahepatic portosystemic shunt in place, one withdrew consent, and one was withdrawn by the investigator because of a previous cerebrovascular accident. A flow diagram of patient allocation is outlined in Figure 1.

Baseline characteristics were similar between treatment groups (Table 1). Findings at first endoscopy and characteristics of endoscopic and vasoactive therapy are summarized in Table 2. Bleeding was found to be of variceal origin in 68% of patients in the placebo

Table 1. Baseline Characteristics

	Placebo N = 121	rFVIIa N = 121
Age (yr)	54.2 ± 10.6	52.6 ± 11.9
Male (no.)	90 (74%)	90 (74%)
Index bleed of variceal origin (no.)	82 (68%)	79 (65%)
Child-Pugh score	8.4 ± 1.9	8.1 ± 2.0
Child-Pugh grade (no.)		
A (scores 5–6)	23 (19%)	23 (19%)
B (scores 7–9)	58 (48%)	66 (55%)
C (scores 10–13)	38 (31%)	29 (24%)
Prothrombin time (s) ^a		
A (scores 5–6)	15.0 ± 2.1	15.4 ± 2.9
B (scores 7–9)	18.0 ± 3.0	17.9 ± 4.2
C (scores 10–13)	28.2 ± 21.5	25.9 ± 8.8
Systolic blood pressure (mm Hg)	124 ± 23	118 ± 21
Heart rate (beats/min)	95 ± 21	96 ± 20
Alcohol-induced-cirrhosis (no.)	81 (67%)	88 (73%)
Hematocrit (%)	27.4 ± 7.2	27.3 ± 7.0
Hemoglobin (g/dL)	9.2 ± 2.5	9.2 ± 2.4
Platelet count (×10 ⁹ /L)	103.3 ± 58.4	110.8 ± 60.9
Alanine transaminase (U/L)	22.1 ± 32.4	15.8 ± 17.5
Alkaline phosphatase (U/L)	197.8 ± 147.5	158.3 ± 98.7
Creatinine (mg/dL)	0.9 ± 0.4	1.0 ± 0.4

NOTE. Continuous variables and Child-Pugh score are presented as mean ± SD.

^aEvaluated at baseline for 213 patients.

group and in 65% of patients in the rFVIIa group. In total, 83% of rFVIIa-treated patients and 88% of placebo-treated patients received concomitant vasoactive treatment to control bleeding. There was no difference between treatment groups in the proportion of patients who were bleeding actively at first endoscopic procedure. The initial endoscopic procedure was performed 2.2 ± 2.5 hours (mean ± SD) and 2.1 ± 2.6 hours after first dosing of trial product in patients receiving placebo and rFVIIa, respectively. Time elapsed from admission (or index bleed if already hospitalized) to initial endoscopy was 7.8 ± 6.9 hours and 7.2 ± 5.4 hours in placebo-dosed and rFVIIa-dosed patients, respectively.

Efficacy

Results of therapy are presented in Table 3. Overall, no effect was observed on the composite end point or on its components. However, a trend toward a decrease of the failure rate was observed in patients bleeding from varices and treated with rFVIIa (8 of 78 vs. 16 of 80; relative risk reduction, 0.49; *P* = 0.12). This trend for a beneficial effect of rFVIIa was consistent across the components of the composite end point except for mortality (Table 3). Moreover, an exploratory analysis of the subgroup of variceal bleeders with Child–Pugh scores B or C and more severe coagulopathy indicated that significantly fewer rFVIIa-treated patients than placebo-treated patients failed on the

composite end point (15 failures in 64 placebo-treated patients vs. 5 failures in 62 rFVIIa-treated patients; *P* = 0.03) and the 24-hour bleeding control end point (7 failures in 63 placebo-treated patients vs. 0 failures in 62 rFVIIa-treated patients; *P* = 0.01), whereas a trend was observed for the prevention of rebleeding end point (8 failures in 61 placebo-treated patients vs. 3 failures in 62 rFVIIa-treated patients; *P* = 0.13). The observed failure rates were higher with rFVIIa than with placebo in patients in whom the source of bleeding was either unconfirmed or not of variceal origin (8 of 42 rFVIIa-treated patients and 3 of 39 placebo-treated patients). No effect of treatment was observed for mortality.

A minority of patients could not be assessed on failure end points, primarily because they withdrew consent or were lost to follow-up evaluation on or before day 5. To test the robustness of the earlier-described findings and to assess the potential impact of this loss of information, best-case and worst-case scenarios with respect to failure scoring for these nonassessable patients were constructed and the corresponding *P* values were calculated. Only a minor influence was observed, with significant *P* values still being borderline statistically significant for the worst-case scenarios (Table 4).

Child–Pugh grade was the only significant covariate in the applied logistic regression models for the primary com-

Table 2. Findings at First Endoscopy and Characteristics of Therapy

	Placebo N = 121	rFVIIa N = 121
Source of bleeding		
Esophageal varices	77 (64%)	68 (56%)
Gastric varices	5 (4%)	11 (9%)
Gastric ulcer	9 (7%)	12 (10%)
Mallory Weiss tear	5 (4%)	12 (10%)
Portal hypertensive gastropathy	10 (8%)	5 (4%)
Other	12 (10%)	7 (6%)
Unknown	3 (2%)	6 (5%)
Type of bleeding		
Spurting	20 (17%)	16 (13%)
Oozing	50 (41%)	51 (42%)
No active bleeding	51 (42%)	54 (45%)
Type of endoscopic therapy		
Sclerotherapy and banding	3 (2%)	3 (2%)
Sclerotherapy only	37 (31%)	37 (31%)
Banding only	40 (33%)	32 (26%)
None	39 (32%)	46 (38%)
Vasoactive therapy		
Octreotide	25 (21%)	29 (24%)
Somatostatin	34 (28%)	33 (27%)
Terlipressin	13 (11%)	7 (6%)
More than one vasoactive drug	35 (29%)	32 (26%)
No vasoactive therapy	14 (12%)	20 (17%)
Proton pump inhibitor therapy	104 (86%)	109 (90%)

NOTE. Data refer to number and percentage of patients.

Table 3. Results of Therapy

	Placebo N = 121	rFVIIa N = 121	P value
	Failures/scored patients ^a		
Failure on composite end point			
All patients (primary end point)	19/119 (16%)	16/118 (14%)	0.72
Variceal bleeders	16/80 (20%)	8/78 (10%)	0.12
Variceal bleeders Child-Pugh B–C ^b	15/64 (23%)	5/62 (8%)	0.03
Failure to control bleeding within 24 hours			
All patients	10/119 (8%)	6/120 (5%)	0.31
Variceal bleeders	8/80 (10%)	2/78 (3%)	0.10
Variceal bleeders Child-Pugh B–C ^b	7/63 (11%)	0/62 (0%)	0.01
Failure to prevent rebleeding (24 h–day 5)			
All patients	10/116 (9%)	9/116 (8%)	1.00
Variceal bleeders	9/77 (12%)	5/77 (6%)	0.40
Variceal bleeders Child-Pugh B–C ^b	8/61 (13%)	3/62 (5%)	0.13
Mortality			
Deaths within 5 days	4/119 (3%)	7/118 (6%)	0.38
Deaths within 42 days	11/120 (9%)	16/116 (14%)	0.31
Red blood cell requirements (units; mean ± SD)			
Within 24 hours	0.7 ± 1.2	0.9 ± 1.8	0.51
Within 5 days	1.3 ± 1.9	1.5 ± 3.7	0.73
Active bleeding at first endoscopy			
All patients	45/121 (37%)	47/119 (39%)	0.79
Variceal bleeders	33/82 (40%)	33/79 (42%)	0.87

^aRatios represent number of failures relative to the total number of patients for whom data were available for evaluation as either failure or success.

^bExploratory end points.

posite failure end point. Cox regression analyses showed that Child–Pugh grade, but not trial product treatment, significantly influenced time to death within 42 days and time to rebleeding within 42 days (data not shown).

No significant effect of treatment was observed for requirement for red blood cells (Table 3), or for number of emergency and elective procedures performed (data not shown). Likewise, no consistent effect of treatment

was observed with respect to the number of days spent in the intensive care unit or hospital.

Normalization of prothrombin time was observed in the majority of patients after rFVIIa dosing (Figure 2).

Safety

Overall, 95 of 121 patients in the placebo group had 288 adverse events of which 67 were seri-

Table 4. Sensitivity Analyses of Failure End Point Outcomes

	Worst-case scenario ^a			Best-case scenario ^a		
	Placebo	rFVIIa	P value	Placebo	rFVIIa	P value
Failure on composite end point						
All patients (primary end point)	19/121	19/121	1.00	21/121	16/121	0.48
Variceal bleeders	16/82	9/79	0.19	18/82	8/79	0.05
Variceal bleeders Child-Pugh B–C ^a	15/65	6/63	0.06	16/65	5/63	0.02
Failure to control bleeding within 24 hours						
All patients	10/121	7/121	0.62	12/121	6/121	0.22
Variceal bleeders	8/82	3/79	0.21	10/82	2/79	0.03
Variceal bleeders Child-Pugh B–C ^a	7/65	1/63	0.06	9/65	0/63	<0.01
Failure to prevent rebleeding (24 h–day 5)						
All patients	10/121	14/121	0.52	15/121	9/121	0.28
Variceal bleeders	9/82	7/79	0.79	14/82	5/79	<0.05
Variceal bleeders Child-Pugh B–C ^a	8/65	4/63	0.37	12/65	3/63	0.03
Mortality						
Deaths within 5 days	4/121	10/121	0.17	6/121	7/121	1.00
Deaths within 42 days	11/121	21/121	0.09	12/121	16/121	0.55
Active bleeding at first endoscopy						
All patients	45/121	49/121	0.69	45/121	47/121	0.90
Variceal bleeders	33/82	33/79	0.87	33/82	33/79	0.87

^aFor the worst-case scenario, nonassessable patients in the placebo group and rFVIIa group were scored as successes and failures, respectively, vice versa for the best-case scenario.

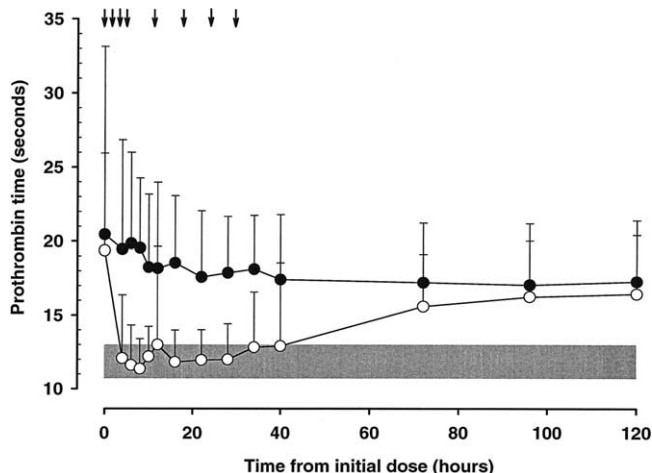


Figure 2. Prothrombin time (mean and SD) by treatment group. ●, Placebo-dosed patients; ○, rFVIIa-dosed patients. Arrows indicate time of dosing. Normal range is defined by the gray shaded area.

ous, and 84 of 121 patients in the rFVIIa group had 249 adverse events of which 55 were serious. A total of 14 thromboembolic adverse events were recorded during the trial, 7 in each treatment group. These events included 8 clinically asymptomatic events of portal vein thrombosis (5 in the placebo group and 3 in the active group) diagnosed through elective Doppler examinations; 3 events of phlebitis (2 in the placebo group and 1 in the rFVIIa group); and 1 nonserious event of thrombosis (blood clot in the central catheter) in the rFVIIa group on the last day of trial product administration, from which the patient recovered completely. Furthermore, 2 cerebrovascular events occurred after repeated dosing with rFVIIa. A right-hemisphere cerebrovascular accident occurred in a 58-year-old man; the patient recovered with resultant mild neurologic sequelae. The patient smoked 20 cigarettes daily and was abusing alcohol actively; a computed tomography scan 3 months before the event showed lesions suggestive of a previous infarction in the right cerebral hemisphere. A cerebral infarction occurred in a 73-year-old man, who died from the event. The patient was a nonsmoker without active alcohol abuse, but the patient suffered from arterial hypertension.

D-dimer, prothrombin fragment 1+2, and thrombin-antithrombin complex (markers of thrombin formation) increased significantly more in patients receiving rFVIIa relative to placebo when analyzing change from baseline to 40 hours after first dose (ANOVA; all P values < 0.0001), which is consistent with the pharmacologic effect of rFVIIa. No effect of dosing on platelet count was observed from repeated-measure ANOVA, and mean

fibrinogen concentrations were within the lower end of the normal range for all time points (data not shown).

Discussion

This trial was designed to investigate whether rFVIIa could improve control of acute UGIB in cirrhotic patients when administered as add-on to standard therapy. Definitions of failure to control bleeding end points adhered to the Baveno II criteria,¹⁶ except that the use of balloon tamponade was added as a failure criterion.

Although no effects of rFVIIa treatment were detected for the total patient population, a consistent trend toward a decrease in the rate of failure on bleeding end points was evident in patients with variceal bleeds receiving rFVIIa. Analyses were performed post hoc on variceal bleeders stratified by Child-Pugh grade (grade A vs. grades B or C) to examine the ability of rFVIIa to compensate for coagulopathies induced by varying degrees of cirrhosis. Statistically significant reductions in failure rates for the composite and 24-hour bleeding control end points then were observed with rFVIIa treatment in the subgroup of variceal bleeders with advanced cirrhosis and more severe coagulopathy (Child-Pugh classes B or C). The finding that the effect of rFVIIa treatment was most pronounced in variceal bleeders who had moderate to severe cirrhosis is consistent with the ability of rFVIIa to correct coagulopathy, which was indeed confirmed by this study. Further studies are required to better define the target population that may benefit the most from rFVIIa treatment and to establish the minimal effective dosing regimen and pharmacoeconomics for this drug.

In patients in whom the source of bleeding was either not established or not of variceal origin, the failure rate seemed to be higher with rFVIIa (8 of 42 [19%] patients) than with placebo (3 of 39 [8%] patients). Specifically, within the group of patients for whom site of bleeding could not be established, failure on the primary end point occurred in 5 of 7 patients receiving rFVIIa (in 2 of these patients, determination of bleeding site was not possible owing to massive hemorrhage at first endoscopy), but only in 1 of 5 patients receiving placebo. These findings may be coincidental, and it should be noted that an anticoagulant effect of rFVIIa is highly unlikely and has not been observed previously in any clinical setting.

The decrease of failure rates observed in this study was not reflected in the number of units of red blood cells administered in any of the subgroups of patients. This is likely to reflect the low number of patients with very high transfusion requirements, which among other fac-

tors may have been a consequence of (1) the conservative transfusion policy followed in this study in accordance with recent findings²⁰ and recommendations,²¹ (2) the fact that patients who are exsanguinating are unlikely to enter into a randomized clinical trial,²² and (3) the early use of vasoactive drugs in the majority of patients in this trial, which has been shown to decrease transfusion requirements.^{23–25}

Mortality as a consequence of the initial bleeding episode is reportedly on average about 30%,^{2,26,27} stressing the importance of achieving initial control of bleeding and preventing early rebleeding. In the present study, initial control of bleeding was achieved in 93% of patients, early rebleeding was prevented in 92% of patients, and overall 5-day and 6-week mortality was 5% and 11%, respectively. These success rates attest to the high efficacy of standard treatment at the participating centers, but are also a consequence of the exclusion from the trial of patients with a Child–Pugh score of ≥ 12 . For these reasons, the statistical power to verify reductions in failure end points was less than anticipated. The failure rate on the composite end point was only 16% in the placebo group, whereas the power calculation for the trial was based on a placebo failure rate of 30%.

When administering a procoagulant drug such as rFVIIa, concerns might be raised that patients could be at a higher risk for developing thromboembolic complications. However, there was no difference in the prevalence of thromboembolic complications between the 2 treatment groups. Portal vein thrombosis was diagnosed in 2% (3 of 121) of patients receiving rFVIIa and 4% (5 of 121) of patients receiving placebo. The previously reported incidence of portal vein thrombosis in cirrhosis ranges from 0.6% to 14%.^{2,28} Moreover, no signs of systemic activation of the coagulation cascade were observed from coagulation-related laboratory parameters or clinical signs. This may be explained by the mode of action of rFVIIa: the hemostatic effect of rFVIIa at pharmacologic doses appears to be mediated by enhancing thrombin generation on activated platelets accumulated at the site of vessel injury.^{11,29,30} Given this localized effect of rFVIIa, an increased incidence of thrombotic complications or intravascular coagulation after dosing with rFVIIa would not be expected. This is supported by the low incidence of thromboembolic events within the currently approved indications.³⁰

In conclusion, this initial trial with rFVIIa in UGIB suggests that rFVIIa can be used safely in this clinical setting. Although no overall effects were detected, the subgroup of patients with variceal bleeds and with moderate to advanced cirrhosis is likely to benefit from

rFVIIa treatment. Further studies are warranted to verify these findings.

Appendix

European Study Group on rFVIIa in UGI Hemorrhage

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