Recombinant factor VIIa for variceal bleeding in liver cirrhosis: still only a hope

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At present, recombinant activated coagulation factor VII (rFVIIa) is approved for the treatment of hemophilia A and B [1, 2]. The use of rFVIIa may also be considered as an adjunctive treatment option for blunt trauma, post-partum hemorrhage, uncontrolled bleeding in surgical patients, and bleeding after cardiac surgery [3]. However, the use of rFVIIa for the treatment of upper gastrointestinal bleeding remains controversial, especially in cirrhotic patients. Several small-scale studies suggest that rFVIIa can effectively correct the coagulation status in patients with liver diseases without any severe adverse events, thereby decreasing the risk of bleeding related to percutaneous approaches, such as liver biopsy (Table I) [4–8]. On the other hand, rFVIIa can achieve hemostasis in patients with liver cirrhosis [9]. A small case series reported by Romero-Castro et al. analyzed the hemostatic efficacy of 4.8 mg rFVIIa in 8 cirrhotic patients with severe active bleeding from esophageal varices [7]. The rates of hemostasis, rebleeding, and mortality were 100% (8/8), 25% (2/8), and 50% (4/8), respectively. However, two multicenter, double-blinded, randomized controlled trials (RCTs) by Bosch et al. achieved negative results regarding the efficacy and safety of rFVIIa for the treatment of upper gastrointestinal bleeding (UGIB) in cirrhotic patients [10, 11].

In the first RCT, 245 cirrhotic patients with active UGIB requiring hospitalization and volume replacement therapy were randomized into the rFVIIa and placebo groups between April 2001 and April 2002 [10]. The source of UGIB was variceal in 66% of patients, non-variceal in 29%, and unknown in 5%. Among them, 118 patients treated with rFVIIa and 119 patients treated with placebo were finally analyzed for the primary outcome. A composite primary endpoint was composed of the failure to control acute bleeding within 24 h after the first dose of trial product, failure to prevent rebleeding between 24 h and 5 days, and death over a 5-day trial period. The overall analysis found that the primary endpoint was not significantly different between rFVIIa and placebo groups (14% (16/1180) vs. 16% (19/119), \( p = 0.72 \)). The subgroup analysis of a high-risk population (i.e., variceal bleeders with Child-Pugh class B-C) demonstrated that the rate of primary endpoint was significantly higher in the rFVIIa group than in the placebo group (8% (5/62) vs. 23% (15/64), \( p = 0.03 \)). Accordingly, it was concluded that rFVIIa might be effective for cirrhotic patients with variceal bleeding and Child-Pugh class B-C, but not for those with non-variceal UGIB and/or mild liver dysfunction.
Table 1. Use of rFVIIa to correct the coagulopathy

| First author, journal (year) | Country | Study design | Target population | No. patients | Periods | Drugs | Efficacy | Safety |
|-----------------------------|---------|--------------|-------------------|--------------|---------|-------|----------|--------|
| Bernstein, Gastroenterology (1997), full-text | Denmark | A preliminary, single-center dose-escalation trial | Cirrhotic patients with Child-Pugh B or C and a PT of ≥ 2 s above the upper limit of the reference value after an intramuscular injection of vitamin K | 10 | 1995.2–1995.3 | rFVIIa (5, 20, and 80 mg/kg) | The mean PT transiently corrected to normal in all three dosage groups | No adverse events |
| Ejlersen, Scand J Gastroenterol (2001), full-text | Denmark | A single-centre, open-label pilot trial | Patients with alcoholic liver diseases who had oesophageal variceal bleeding and a prolonged PT | 10 | NA | One intravenous injection of rFVIIa (80 mg/kg body weight) | Immediate bleeding control was obtained in all patients. PT normalized in all patients 30 min after injection of rFVIIa | No adverse events |
| Petersson, Hepatology (2001), abstract | Sweden | NA | Children with chronic liver disease; with life-threatening bleeding and failed conventional therapy in 7 patients (19 occasions) and prophylaxis before liver biopsy in 6 patients (9 occasions) | 12 | 1999.5–2001.4 | An intravenous bolus dose of 36–118 μg/kg or 54–163 μg/kg | All patients responded to the treatment with an effect on INR | No obvious adverse events |
| Jeffers, Gastroenterology (2002), full-text | USA | An open label pilot run-in (part I); and a multicenter, randomized, double-blind trial (part II) | Cirrhotic patients with Child-Pugh B or C, platelet count > 60,000/mm³; PT in the range of 3–15 s above normal, and before laparoscopic liver biopsy | 71 | NA | rFVIIa (5, 20, 80, and 120 g/kg body weight) | PT was corrected to normal levels (< 13.1 s) in the majority of patients | No adverse events related to rFVIIa |
| Sajjad, Dig Dis Sci (2009), full-text | USA | NA | Consecutive individuals with advanced disease-induced coagulopathy or a therapeutic-induced coagulopathy; the use of fresh-frozen plasma was deemed inappropriate | 33 | NA | A dose of 100 μg/kg of rFVIIa over 2 min | The mean PT was transiently corrected in these subjects | No severe adverse events |

INR – international normalized ratio, NA – not available, PT – prothrombin time.
Based on the findings from the first RCT [10], the investigators selected the cirrhotic patients with Child-Pugh class B and C and variceal bleeding for the second RCT [11]. Between April 2004 and August 2006, a total of 256 subjects were randomized into the placebo (n = 85), 300 μg/kg rFVIIa (n = 85), and 600 μg/kg rFVIIa (n = 85) groups [11]. All of them had a Child-Pugh score of > 8 points (Child-Pugh B/C: 26%/74%). The primary endpoint was the treatment failure according to the Baveno II–IV criteria, including the failure to control acute bleeding within 24 h, failure to prevent clinically significant rebleeding, or death within 5 days. The rate of primary endpoint was similar between placebo and 600 μg/kg rFVIIa groups (23% (20/86) vs. 20% (17/85); odds ratio = 0.8, 95% confidence interval: 0.29–0.97, p = 0.04) [14]. Notably, the upper limit of the 95% confidence intervals was close to 1. In addition, only a fixed-effects model was employed according to the result of the χ² test for the heterogeneity (p = 0.12). But the value of I² = 59% might be neglected. As is well known, the choice of a fixed-effects or random-effects model often depends on the statistical significance of heterogeneity among studies. When p < 0.1 or I² > 50% is obtained, a random-effects model is considered appropriate. In addition, when a random-effects model is employed to update the meta-analysis, the statistical significance disappears (odds ratio = 0.35, 95% confidence interval: 0.06–2.00, p = 0.24) (Figure 1).

In conclusion, apart from its marginal efficacy in the treatment of variceal bleeding, we should never neglect that rFVIIa is too expensive and may increase thromboembolism without any significant survival benefits [18–20]. Accordingly, the use of rFVIIa may not be recommended in cirrhotic patients with acute variceal bleeding until positive findings from high-quality studies are reported in a selected population.

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**Figure 1.** Forest plot of meta-analysis regarding the benefit of rFVIIa for the 5-day failure rate in cirrhotic patients with active variceal bleeding and a Child-Pugh score > 8 using a random-effects model

| Study or subgroup | rFVIIa | Placebo | Weight (%) | Odds ratio (M-H, random, 95% CI) | Odds ratio (M-H, random, 95% CI) |
|------------------|--------|---------|------------|-------------------------------|-------------------------------|
| AVHC 1288        | 1      | 11      | 8          | 16                            | 32.5                          |
| AVHC 1533        | 28     | 170     | 20         | 86                            | 67.5                          |
| Total (95% CI)   | 181    | 102     | 100        | 0.35 (0.06–2.00)               |
| Total events     | 29     | 28      |            |                               |

Heterogeneity: τ² = 1.05, χ² = 2.44, df = 1 (p = 0.12), I² = 59%

Test for overall effect: Z = 1.18 (p = 0.24)
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Conflict of interest

The authors declare no conflict of interest.

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