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 I. 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/mm^3, 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 = 86), 600 µg/kg rFVIIa (n = 85), and 300 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, p = 0.37). Notably, the patients treated with 300 µg/kg rFVIIa had a lower rate of composite endpoint (13% (11/85)). However, the investigators did not compare the efficacy between 300 µg/kg rFVIIa and placebo groups according to the statistical analysis plan. Herein, we used the raw data to re-calculate the statistical significance by using a χ^2 test, but the difference was not significant (23% (20/86) vs. 13% (11/85), p = 0.080). Accordingly, the previous conclusion achieved by the subgroup analysis of the first RCT was not supported, because rFVIIa had no significant effect on the primary composite endpoint in high-risk patients.

Marti-Carvajal *et al.* conducted a Cochrane systematic review and meta-analysis of the two RCTs to analyze the outcome of rFVIIa for UGIB in patients with liver diseases [12, 13]. Compared with placebo, rFVIIa did not reduce the risk of 5- and 42-day mortality or increase the risk of adverse events (neither serious adverse events nor thromboembolic events were not significantly different between the two groups). Thus, the systematic reviewers did not find any evidence to accept or reject the use of rFVIIa for UGIB in patients with liver diseases.

Despite this, the investigators did not give up the idea of rFVIIa for bleeding in liver cirrhosis. More recently, Bendtsen *et al.* conducted a meta-analysis of the individual patient data from the two previous RCTs [14]. Notably, the 5-day failure rate was significantly lower in cirrhotic patients with active bleeding at endoscopy and a Child-Pugh score > 8 receiving rFVIIa than in those receiving placebo (odds ratio = 0.53, 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 χ^2 test for the heterogeneity (p = 0.12). But the value of I^2 = 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 I^2 > 50% is obtained, a random-effects model is considered appropriate. Indeed, 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 addition, the overall meta-analysis by Bendtsen *et al.* failed to support any significant treatment effect in the intention-to-treat population, but the subgroup meta-analysis achieved a statistical significance in patients with active variceal bleeding at endoscopy, especially in those with a Child-Pugh score > 8 [14]. However, the tests for interaction were not performed among different subgroups. Given that chance could create the imbalance among subgroups, the credibility of the subgroup analysis might be overestimated [15]. The validity of subgroup effects should be assessed to avoid potentially misleading or biased conclusions [16, 17]. Similarly, the subgroup analysis of the first RCT found a significant benefit of rFVIIa in the high-risk population [10], but the overall analysis of the second RCT did not support the finding [11]. Therefore, the results of the subgroup analyses should be cautiously interpreted due to their methodological limitations.

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.

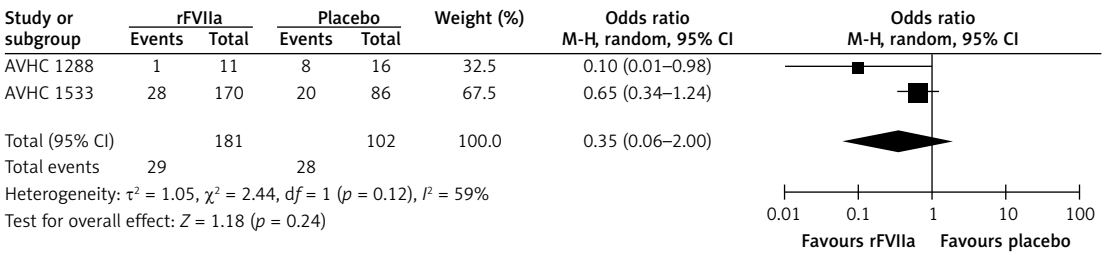

Figure 1. Forest plot of meta-analysis regarding the benefit of rFVIIa for the 5-day failure rate in cirrhotic patients with active variceal bleeding and a Child-Pugh score > 8 using a random-effects model

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The first two authors contributed equally to this work.

Conflict of interest

The authors declare no conflict of interest.

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