Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Effect of recombinant Factor VIIa on outcome of acute variceal bleeding: An individual patient based meta-analysis of two controlled trials

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Background & Aims: Two randomized controlled studies have evaluated the effect of recombinant Factor VIIa (rFVIIa) on variceal bleeding in cirrhosis without showing significant benefit. The aim of the present study was to perform a meta-analysis of the two trials on individual patient data with special focus on high risk patients.

Methods: The primary outcome measure was the effect of rFVIIa on a composite five day endpoint: failure to control bleeding, 5-day rebleeding or death. Analysis was based on intention to treat. High risk was defined as active bleeding on endoscopy while under vasoactive drug infusion and Child-Pugh score >8.

Results: 497 patients were eligible for the meta-analysis; 308 (62%) had active variceal bleeding at endoscopy (oozing or spurting) and 283 of these had a Child-Pugh score >8. Analysis on the composite endpoint in all patients with bleeding from oesophageal varices did not show any beneficial treatment effect. However, failure rate for the primary composite end-point was significantly lower in treated patients with active bleeding at endoscopy (17%) compared to placebo (26%, $p = 0.049$). This difference was highly significant in patients with Child-Pugh score >8 and active bleeding at endoscopy (rFVIIa 16%, placebo 27%; $p = 0.023$). No significant treatment effect was found at 42 days. Five thromboembolic events occurred in rFVIIa treated patients compared to none in placebo treated patients.

Conclusions: The current meta-analysis shows a beneficial effect of rFVIIa on the primary composite endpoint of control of acute bleeding, prevention of rebleeding day 1–5 and 5-day mortality in patients with advanced cirrhosis and active bleeding from oesophageal varices at endoscopy. A major drawback of the treatment is a potential increased risk of arterial thrombo-embolic events. This treatment might be considered in patients with lack of control of bleeding after standard treatment.

Introduction

The management of variceal bleeding in cirrhosis remains a clinical challenge although mortality has decreased from 42% [1] to 15–20% in the last 3 decades [2,3]. Combined pharmacological and endoscopic therapy is currently the standard of care [4,5], although early TIPS should be considered in high risk patients with active bleeding at endoscopy [6]. In patients with advanced cirrhosis, the synthesis of coagulation factors is decreased, notably factor VII, which can be corrected by infusion of rFVIIa (NovoNordisk A/S Denmark) [7].

In a randomized, controlled trial investigating the safety and efficacy of rFVIIa in patients with upper gastrointestinal bleeding and cirrhosis, there was no significant effect of rFVIIa treatment on the number of 5-day failures [8]. However, a posthoc analysis found that rFVIIa significantly reduced the number of 5-day failures and improved 24-h bleeding control in the subgroup of Child-Pugh B and C patients with endoscopic proven active variceal bleeding.

A second study was then performed to investigate the efficacy and safety of rFVIIa in patients with severe liver disease (Child-Pugh score >8 points) and spurting or oozing variceal bleeding at emergency endoscopy [9]. Patients were equally

Keywords: Acute variceal bleeding; Treatment; Outcome; Meta-analysis; Factor rVIIa.

Received 18 October 2013; received in revised form 21 March 2014; accepted 30 March 2014; available online 5 April 2014

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Abbreviations: rFVIIa, recombinant Factor VIIa; ITT, intention to treat; AV, active variceal bleeders at endoscopy; AVCP, Child-Pugh score >8 and active bleeding at endoscopy; AMI, myocardial infarction.

Table 1. Patients by study and treatment.

	Study 1288		Study 1533		All	
Patient group	Placebo	rFVIIa	Placebo	rFVIIa	Placebo	rFVIIa
All patients	123	122	89	176	212	298
ITT patients	121	120	86	170	207	290
Active variceal bleeders	30	22	86	170	116	192
Active variceal bleeders Child-Pugh >8	16	11	86	170	102	181

randomized to different doses of rFVIIa (600 μg/kg administered in four doses or 300 μg/kg administered in two doses) or placebo. It was decided beforehand that the 300 μg/kg would only be compared to placebo in case of a positive outcome of the high dose. No beneficial effect of 600 μg/kg of rFVII was found in 5-day failure. A major limitation of this second study was that the observed failure rate with placebo was actually much lower (23%) than predicted (40%) with loss of power. Moreover there was a marked heterogeneity in the treatment effect across participating centers. In fact, an exploratory analysis revealed a reduced treatment failure rate under rFVIIa administration at both low and high dose in centers with >10% failure rate, which would be in accordance with the results of the previous trial. The conclusion of this second study was that rFVIIa may not be used routinely for the treatment of variceal bleeding. However the aim of this study, which was to test the treatment effect in high risk patients, was not achieved because of some inadvertent patient selection bias and lack of power.

Therefore, the aim of the present study was to perform a meta-analysis of the two trials based on individual patient data with special focus on high risk patients with active bleeding at endoscopy.

Patients and methods

Study design

This is an individual patient based meta-analysis of the two randomized placebo controlled, double blind trials [8,9]. All the patients in the intention to treat (ITT) population from the two studies were included. Safety analysis included severe and total adverse events. A separate analysis has also been performed in two subgroups of patients at higher risk: (a) active variceal bleeding; (b) active variceal bleeding and Child Pugh score >8.

Patients

The two studies were identified as 1288 [8] and 1533 [9] NovoNordisk A/S studies, respectively, and will be identified simply by their identification number or by reference from now on throughout the text of this article. Inclusion criteria were; age ⩾18 and <75 years [8] and <80 [9], cirrhosis with oesophageal or gastric varices or portal hypertensive gastropathy, with Child-Pugh score <12 in study 1288 and >8 in 1533; haematemesis or melaena within 24 h of inclusion, requiring hospital admission and volume replacement therapy in 1288 and endoscopy-proven, active oesophageal or gastro-oesophageal variceal bleeding in 1533.

Exclusion criteria were for both studies: known hypercoagulopathy, acquired FVII deficiency or hereditary bleeding disorder, known HIV infection, history of portal vein thrombosis, history of pulmonary embolism or deep vein thrombosis within 6 months, history of stable/unstable angina pectoris or ECG signs of cardiac ischemia, myocardial infarction, intermittent claudication, or TIA/ischaemic stroke, concomitant diseased subjects with a life expectancy of less than 6 months, grade IV encephalopathy, previous TIPS, previous orthoptic liver transplantation, major surgery within the last 30 days, pregnancy, known GI/respiratory system cancer/hepatocellular carcinoma, subjects taking chemotherapy for cancer, renal insufficiency (serum creatinine >200 μmol/L).

The two studies differed on the following exclusion criteria. Patients were excluded if the patient had undergone sclerotherapy or band ligation of oesophageal varices within the previous 6 weeks in study 1288 and in study 1533 only if performed within the previous 2 weeks. Patients with bleeding from isolated gastric varices were excluded from study 1533. In study 1288 three patients were not included in the ITT population since they were not dosed. One patient in 1288 was erroneously included without having experienced a bleeding episode (receiving rFVIIa) and due to this was excluded from the ITT population. In study 1533 nine patients were not included in the ITT population since one had Child-Pugh score 8, seven patients did not have active variceal bleedings and one patient because of non-acceptance of protocol amendment by the health authority. In 1288 MELD score (data lacking on 29 with active bleeding) was not a part of the trial plan and due to this MELD score was not included in the analysis plan.

Overall 241 ITT patients from study 1288 and 256 ITT patients from study 1533 have been included in this meta-analysis, totalling 497 patients. A separate analysis was planned for the 308 patients with active variceal bleeding at endoscopy and for the 283 also with a Child-Pugh score 9–15 (Table 1).

Trial treatments and outcome measures of 1288 and 1533 studies

In trial 1288 patients randomised to active treatment received 100 μg/kg bw rFVIIa or placebo administered within 1 h prior to endoscopy and repeated at 2, 4, 6, 12, 18, 24, and 30 h. In trial 1533 patients were equally randomized to the following 3 regimens: (a) 200 μg/kg body weight (bw) rFVIIa within 1 h after endoscopy, followed by 100 μg/kg(bw) rFVIIa at 2, 8, 14, and 20 h after first trial product administration; (b) 200 μg/kg(bw) rFVIIa followed by 100 μg/kg(bw) rFVIIa at 2 h, followed by placebo at 8, 14, and 20 h after first trial administration; (c) placebo at all the time points. Vasoactive treatment [10–12], endoscopic treatment within 6 h, either ligation or sclerotherapy (if bleeding was of variceal origin) and antibiotics [13] were mandatory treatments in both studies. Patients were monitored closely over the 5-day trial period, with a final follow-up on day 42. Transfusions were given to maintain a target hematocrit of 25–30% [14].

Definitions of treatment efficacy measures

The primary treatment efficacy measure was based on a composite end-point which included: 24-h failure to control acute bleeding and failure to prevent clinically significant rebleeding or death within 5 days after the first trial product administration.

24-h failure to control acute bleeding: new hematemesis together with a reduction in systolic blood pressure ⩾20 mmHg, and/or transfusion of two or more units of blood (whole blood or packed red blood cells) over and above the earlier transfusions required to increase hematocrit to 25–30%. In study 1288 the definition included also a 6-h time point assessment, based on blood transfusion requirement of >4 units.

Clinically significant rebleeding: in study 1288 Baveno II-III [15,16] criteria were used: new hematemesis or new melena and transfusion of two or more units of blood and a change in arterial pressure or pulse rate. The validity of the hemodynamic criteria was later questioned and therefore in study 1533 [17] a clinically significant bleeding was defined by only the first two criteria. In both studies the use of balloon tamponade within 5 days was also considered as failure.

If the definition of rebleeding used in 1533 is applied to the 1288 study there are 12 extra failures regarding rebleeding. However, one of these patients had also a failure according to control of bleeding leading to 11 extra failures in the composite end-point.

Therefore we decided to perform 2 major analyses for the primary endpoint: (1) by using the original failure definition of each study; (2) by applying the failure definition used in trial 1533 to the trial 1288. Secondary treatment efficacy measures for the scope of the present meta-analysis were: 24-h failure to control