

LETTER TO THE EDITOR

Pilot study to test the efficacy and safety of activated recombinant factor VII (NovoSeven) in the treatment of refractory hemorrhagic cystitis following high-dose chemotherapy

Bone Marrow Transplantation (2006) **38**, 825–828.
doi:10.1038/sj.bmt.1705535

Hemorrhagic cystitis (HC) is a known complication of high-dose cyclophosphamide chemotherapy.¹ Approximately 5% of patients undergoing stem cell transplantation (SCT) develop severe HC, which may lead to urinary obstruction, acute renal failure, hydronephrosis, bladder perforation and death.² Treatment of patients with HC is frequently unsatisfactory, and mainly consists of supportive measures.¹

High-dose activated recombinant factor VII (rFVIIa/NovoSeven, NovoNordisk A/S, Bagsværd, Denmark) is a hemostatic agent approved for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors. rFVIIa has been evaluated as a pro-hemostatic agent in a variety of other hemorrhagic conditions,³ including hemorrhage in the setting of SCT.^{4–6} We report the result of a pilot study to test the efficacy of rFVIIa in HC.

Eligible study subjects were between 18 and 65 years of age with severe HC (defined as uncontrolled hematuria with urinary clots and suprapubic pain, with prior exposure to cyclophosphamide or ifosfamide, and without evidence of urinary tract infection), who were unresponsive to (i) optimization of hemostatic parameters and (ii) a trial of at least 24 h of continuous bladder irrigation (CBI). Patients were excluded if they had (a) overt disseminated intravascular coagulation (DIC); (b) myocardial infarction within the previous 3 months, or unstable angina; (c) recent stroke; (d) recent central venous access device-related thrombus; (e) hepatic veno-occlusive disease; (f) history of spontaneous deep vein thrombosis; (g) positive blood culture within the last 7 days; (h) allergic reaction to rFVIIa; (i) pregnancy; (j) topical or systemic antifibrinolytic agents administered in the last 24 h or (k) concurrent granulocyte-macrophage colony-stimulating factor or high-dose estrogen therapy.

rFVIIa in the dose range of 5–120 mcg/kg has been employed in the management of various hemorrhagic conditions and has an elimination half-life of about 3 h.³ Therefore, we elected to administer an initial dose of 80 mcg/kg intravenously (i.v.) followed by up to two additional doses of rFVIIa 120 mcg/kg i.v. administered 3 h apart, if hematuria persisted. All subjects continued standardized gravity-driven high flow CBI. Subjects could receive platelet transfusion 1 h before, and 9 h following the first dose of rFVIIa, but not during the interim. The efficacy of rFVIIa was evaluated by photographically

documenting urine color and assaying urine hemoglobin content by adding diluted (1:10) urine sample to Drabkin's cyanide–ferricyanide solution at 9:1 ratio. Light absorbance at 540 nm was then measured against a blank using a Beckman DU 7500 spectrophotometer. Following the administration of the first dose of rFVIIa, urine samples were collected hourly for the first 9 h, and at 12 and 24 h. Complete response was defined as complete (visual) clearing of hematuria at any time point in the 24-h study period, partial response was defined by visually assessed lightening of urine color; and no response was defined as no change in the urine color. Subjects were monitored for serious adverse events (including venous or arterial thrombosis, laboratory evidence of DIC, cardiac ischemia, hepatic or renal dysfunction) for 5 days after enrollment. Additionally, we measured factor VII activity (FVII:C), whole blood tissue factor activity (TF),⁷ antithrombin III (ATIII) and protein C (PC) chromogenic activities at baseline to evaluate for any correlation with severity (FVII:C), response (TF, FVII:C) and thrombotic complications (ATIII, PC, TF). Descriptive statistical methods were employed to summarize demographic, safety and efficacy data. Binomial probability was computed for the number of responses to the total number of study participants to test for significance, assuming a 20% 'spontaneous' remission rate. This assumption is very conservative, given that these subjects had failed a 24-h trial of CBI and optimization of hemostatic parameters. The study protocol was approved by the Institutional Review Boards of each participating center.

Seven (four female) subjects were enrolled in the study (Table 1). The median age of participants was 33 (range 19–52) years. Six of the seven subjects received all three doses of rFVIIa, whereas one subject received two doses. All subjects had normal baseline ATIII and PC activities. One subject (205) had borderline decreased FVII:C (50%). Six of the seven subjects attained a response (one sided $P=0.0004$); four were complete responses, whereas two were partial responses (see Figure 1). The response duration was temporary in all subjects, with hematuria reverting to an intensity similar to baseline by 24 h. There was no correlation between baseline FVII:C or whole blood TF activity and the degree of response to rFVIIa. No subject experienced a serious adverse event.

This pilot study demonstrates that rFVIIa, at doses of 80–120 mcg/kg, is effective in temporarily abating bleeding in HC with no serious adverse effects. Improvement in hematuria was noted 1–2 h following rFVIIa administration, and subsequent doses yielded additional improve-

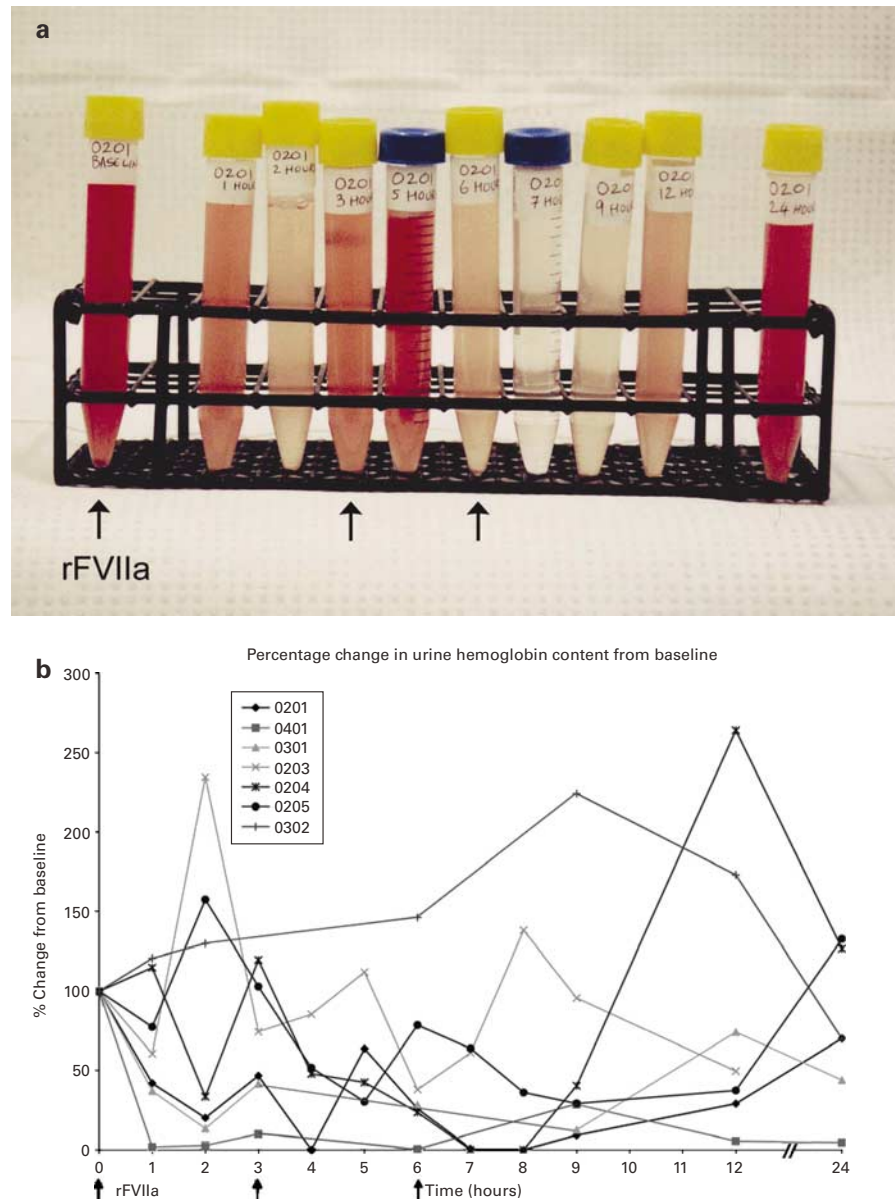


Figure 1 (a) Example of a complete response at 7 h post initiation of rFVIIa in subject 0201. Note that by 24 h, there has been a return to baseline levels of urinary tract bleeding. (b) Percentage change in hemoglobin content from baseline. The arrows represent the times at which rFVIIa was administered.

ment. However, in all patients, the bleeding began to intensify 3–6 h following the last dose of rFVIIa, and was near baseline by 24 h. The short response duration may be due to the short half-life of rFVIIa and/or fibrinolytic dissolution of hemostatic clots in urine.⁸ Therefore, in designing future trials, one should consider multiple doses of rFVIIa, possibly with the addition of an antifibrinolytic agent. However, these agents should be used with caution in any form of hematuria owing to the danger of precipitating urinary tract obstruction.⁹

We believe that the temporary clinical response was due to the hemostatic effect of rFVIIa, as subjects had failed to respond to optimized supportive measures before enrollment. Furthermore, the high flow rate of CBI was constant

throughout the study period for a given subject, and the clearing of hematuria was temporally related to rFVIIa administration, while return of urinary bleeding occurred following the expected pharmacological disappearance of rFVIIa. However, the observed urine color changes may, to some extent, be affected by the subject's fluid intake. A strength of our study was the 'real time' objective monitoring of bleeding, which is difficult or impossible to assess in many other sites. However, the routine use of rFVIIa in HC cannot be recommended on the basis of this exploratory study.

The results of our pilot study corroborate the clinical experience of Karimi *et al.*,⁵ who used rFVIIa in four patients with HC, and of Blatt *et al.*,⁴ who noted a transient

Table 1 Baseline patient characteristics and response to rFVIIa

Patient	Age	Sex	Race	Wt.	Reason for SCT	Type of SCT	Hgb	Plts	INR	aPTT	FVII	ATIII	PC	TF	Fib.	D-Dim.	PFI.2	Visual response	Max. OD reduction
201	21	F	Black	49.5	2° MDS	Cord blood	9.8	84	0.93	28	83	82	74	—	528	200	0.9	Complete	100
203	19	M	Caucasian	54.7	2° MDS	Cord blood	9.9	60	1.15	29	—	84	78	21.1	411	565	2	No	62
204	49	F	Caucasian	67.4	Mantle cell lymphoma	Allogeneic	8.7	83	1.04	29	124	106	112	5.7	285	258	1.5	Partial	100
205	33	M	Caucasian	66.2	Lymphoblastic lymphoma	Auto + non-myeloablative allogeneic	10.6	55	1.16	28	50	102	107	3.5	466	856	1.8	Partial	71
301	33	M	Caucasian	75	AML	Allogeneic	9.1	29	1.0	23	82	110	104	7.6	163	258	2.2	Complete	88
302	52	F	Caucasian	74	Mantle cell lymphoma	Allogeneic	11.2	30	1.1	33	60	89	75	0.3	353	876	2.7	Complete	30
401	30	F	Black	108	CML	Allogeneic	9.4	21	0.98	31	77	91	85	1.5	516	449	1.5	Complete	100

Abbreviations: AML = acute myeloid leukemia; aPTT = activated partial thromboplastin time (s) (normal range: 22.99–40.6 s); ATIII = antithrombin III (%) (normal range: 70–130%); CML = chronic myeloid leukemia; D-Dim. = D-Dimer (ng/ml) (normal range: <278 ng/ml); Fib. = fibrinogen (mg/dl) (normal range: 188–383 mg/dl); FVII = factor VII activity (%) (normal range: 50–155%); Hgb = hemoglobin ($\times 10^9/l$); INR = international normalized ratio (normal range: 0.86–1.14); Max OD reduction = maximal percent reduction in haemoglobin content from baseline (calculated from optical density (OD) reduction from baseline; 2° MDS = secondary myelodysplastic syndrome; PC = protein C (%) (normal range: 55–140%); PFI.2 = prothrombin fragment 1.2 (nmol/l) (normal range: 0.4–1.8 nmol/l); Plts = platelet count ($\times 10^9/l$); SCT = stem cell transplant; TF = (whole blood) tissue factor activity (pg/l); Wt. = weight in kilograms. The laboratory values in bold indicate an abnormal laboratory parameter.

response in two patients with HC administered rFVIIa every 4–6 h. In contrast, Pihusch *et al.*⁶ reported no aggregate benefit of rFVIIa in the treatment of various hemorrhagic complications following SCT in a double-blind randomized, placebo controlled study. This study included 26 subjects with mild or moderate HC. It is possible that the lack of efficacy was, in part, due to the 6-h dose interval, and the insensitivity of the bleeding scale used to assess efficacy.

Acknowledgements

The study was funded by NovoNordisk Pharmaceuticals Inc., Princeton, NJ, USA, which also supplied the study drug. Dr Ashrani is a recipient of mentored patient-oriented research career development award (K-23 HL069203) from the National Heart, Lung and Blood Institute, NIH. We would like to thank the research nurse coordinators, Ms Joan Osip at University of Minnesota Medical Center-Fairview, Ms Carol Krasnov at the University of North Carolina, Chapel Hill and Ms Carrie Ma at MD Anderson Cancer Center for their untiring help and support.

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