available at http://ajws.elsevier.com/tcmj

Tzu Chi Medical Journal

Original Article

Clinical Experiences with Recombinant Activated Factor VII for Managing Uncontrolled Hemorrhage in Non-Hemophilic Patients

*Chi-Cheng Li[1,2], Ji-Hung Wang[3], Yen-Ta Huang[4], Han-Yu Huang[4], Tso-Fu Wang[1,2], Sung-Chao Chu[1,2], Chao-Yuan Yao[1,2], Yi-Feng Wu[1,2], Szu-Chin Li[1,2], Kuan-Po Huang[1,2], Wei-Han Huang[1,2], Ming-Ching Shen[5], Ruey-Ho Kao[1,2]**

[1]*Department of Oncology/Hematology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan*
[2]*Department of Oncology, Tzu Chi University, Hualien, Taiwan*
[3]*Department of Cardiovascular Disease, Buddhist Tzu Chi General Hospital, Hualien, Taiwan*
[4]*Department of Medical Intensive Care Unit, Buddhist Tzu Chi General Hospital, Hualien, Taiwan*
[5]*Department of Oncology/Hematology, Changhua Christian Hospital, Changhua, Taiwan*

Article Info

Article history:
Received: April 20, 2007
Revised: May 8, 2007
Accepted: June 13, 2007

Keywords:
Hemophilia
Hemorrhage
Hemostasis
Recombinant factor VIIa (rFVIIa)
Thromboembolism

Abstract

Objective: Recombinant activated factor VII (rFVIIa) is a novel hemostatic agent originally developed to treat hemophilia patients who had developed inhibitors with bleeding. Its role in treating uncontrolled bleeding in patients without pre-existing coagulation abnormalities has not been well established. We herein report our experiences with its use in non-hemophilic patients.

Patients and Methods: Four patients, aged 33 to 94 years, with different underlying diseases were treated with rFVIIa for uncontrolled, life-threatening hemorrhage. rFVIIa was initially administered by intravenous bolus injection at 80–100 μg/kg. Doses were adjusted according to clinical response.

Results: Clinical response with significant hemostasis was evident in three patients after initial treatment. One patient was unresponsive to rFVIIa treatment and died of uncontrolled bleeding. Of those who achieved initial hemostasis, two died of their underlying diseases. One had recurrent bleeding controlled by subsequent multiple doses of rFVIIa, but she died of acute myocardial infarction, a thromboembolic complication that probably arose from the use of rFVIIa.

Conclusion: Our results suggest that rFVIIa could play a role in the management of bleeding other than congenital coagulation disorder. However, clinical hemostatic effects that do not translate into a survival benefit require further study, especially with regard to appropriate timing for clinical use. Its potential risk, especially that of thromboembolism when treating bleeding in elderly patients, warrants further investigation. (*Tzu Chi Med J* 2007;19(4):220–225)

*Corresponding author. Department of Oncology/Hematology, Buddhist Tzu Chi General Hospital, 707, Section 3, Chung-Yang Road, Hualien, Taiwan.
E-mail address: rueyhokao@tzuchi.org.tw

1. Introduction

Since Hedner et al's introduction of recombinant activated factor VII (rFVIIa) in 1988 (1), it has been observed that high doses of rFVIIa can dramatically stop bleeding in hemophilic patients with inhibitors (2,3), acquired hemophilia (4), congenital factor VII deficiency (5), and even in patients with Glanzmann's thrombasthenia (6). In contrast to the conventional concept of normal hemostasis, in which platelets and plasma proteins act on different pathways, the newly developed cell-base model of coagulation suggests that initiation of a coagulation cascade starts from the binding of factor VIIa to tissue factor (TF) (7,8). Initially, a small amount of thrombin is formed through the activation of factor X by TF-VIIa complex. Although not sufficient to form a fibrin clot, this small concentration of thrombin further activates factors V, VIII, XI and, most importantly, platelets. Secondly, on the surface of activated platelets, the TF-VIIa complex activates factor IX, which in association with the activated forms of factors VIII, X and V, generates adequate amounts of thrombin, which subsequently change soluble fibrinogen to insoluble fibrin clots. It has been shown that administration of a supraphysiological high dose of rFVIIa can act by bypassing the factor VIII/IX pathway to create faster and much higher thrombin generation on the surface of activated platelets that adhere to the site of injury. This TF-independent bypassing mechanism is able to mount a robust hemostasis effect in hemophilic patients with inhibitors or other coagulopathy-related hemorrhages.

In recent years, there has been increasing interest in the use of rFVIIa to treat bleeding in non-hemophilic patients (9). Some reports have been published that record the use of rFVIIa in patients with major bleeding where there is no pre-existing inherited bleeding disorder (10–14). Here, we present our experience with using rFVIIa to treat four patients with no congenital bleeding disorder who presented with clinically uncontrolled hemorrhage.

2. Patients and methods

There were two female and two male patients, aged 33–94 years, with life-threatening bleeding and different underlying diseases other than hemophilia or other congenital coagulation disorders. Recombinant factor VIIa (NovoSeven^{R}; NovoNordisk A/S, Bagsvaerd, Denmark) was administered by intravenous bolus injection at least 2 hours apart. Clinical hemostatic response was classified as effective, partially effective and ineffective as evaluated for hemophilic patients (3). An effective response was defined as bleeding stopping within 8–14 hours of treatment. A partially effective response was defined as bleeding stopping or significant slowing of the hemorrhage after 14 hours of treatment. No clinical hemostatic effect was defined as an ineffective response.

3. Results

The clinical manifestations and treatment outcomes for the four patients are summarized in Table 1 and described in detail below.

3.1. Case 1

An 84-year-old woman who had been generally healthy was found to have hypovolemic shock after an episode of massive coffee-ground vomiting and tarry stool passage. Endoscopic examination disclosed an active gastric ulcer with bleeding. Laboratory data showed white blood cell count (WBC) 7300/μL, hemoglobin 6.0g/dL, and platelet count 21,000/μL. The drop in hemoglobin and platelet count was initially thought to be due to bleeding. However, the platelet count remained at low levels (34,000–42,000/μL) even after endoscopic hemostatic procedures and platelet transfusion. A bone marrow examination was performed and myelodysplastic syndrome was confirmed based on morphological and flow cytometric analysis.

Table 1 — Patient characteristics and treatment outcomes from rFVIIa

Case	Age (yr)	Sex	Underlying disorders	Bleeding sites	rFVIIa (μg/kg)	Doses	Hemostatic response	Cause of death
1	84	F	MDS with thrombocytopenia, pneumonia	GI tract, oral mucosa, venous puncture sites	90, 45	2	Effective	Pneumonia
2	33	M	CML s/p BMT, CMV pneumonia	Lung	80, 100	2	Partially effective	CMV pneumonia
3	94	F	CRF, GI bleeding	GI tract	100	7	Partially effective	AMI
4	46	M	Oral cancer	Small intestine	85	2	Ineffective	Intractable bleeding

MDS = myelodysplastic syndrome; CML = chronic myeloid leukemia; BMT = bone marrow transplantation; CMV = cytomegalovirus; CRF = chronic renal failure; GI = gastrointestinal; AMI = acute myocardial infarction.

Two weeks later, her condition was complicated by hospital-acquired pneumonia, which resulted in respiratory failure. The pneumonia progressed to acute respiratory distress syndrome (ARDS) and caused further reduction in platelet count to around 9000–20,000/μL. In addition, bloody oozing from multiple sites was noted, including the endotracheal tube, oral mucosa, venous puncture sites and intermittently recurring tarry stools which were refractory to platelet transfusion and medical treatment. Furthermore, barotrauma occurred due to poor compliance of the lung condition, resulting in right side tension pneumothorax that required emergent chest tube drainage. Laboratory data showed WBC 4500/μL, hemoglobin 7.5 g/dL, platelet count 13,000/μL, prothrombin time (PT) 11.7 seconds (normal range, 9.9–11.6 seconds), and activated partial thromboplastin time (aPTT) 35.7 seconds (normal range, 23.9–34.9 seconds).

Fearing uncontrolled bleeding would result from the invasive procedure of chest tube insertion, one dose of rFVIIa 90 μg/kg was given. Fifteen minutes later, the PT had shortened to 8.2 seconds and aPTT to 32.9 seconds. A chest tube was then smoothly inserted without any bleeding. Meanwhile, her platelet count rose to 79,000/μL for the first time after a transfusion, a response not previously in evidence before rFVIIa administration. The hemorrhage from multiple sites stopped as well. A second half-dose of rFVIIa, of 45 μg/kg, was given the next day before a tracheostomy because of prolonged intubation. Again, no bleeding was evident during and after this invasive procedure. No other adverse effect was seen after rFVIIa injection. Unfortunately, she passed away from worsening pneumonia with septic shock.

3.2. Case 2

The condition of a 33-year-old man with chronic myeloid leukemia was complicated by extensive chronic graft-versus-host disease (GVHD) after receiving allogeneic bone marrow transplantation from his younger sister. The GVHD flared up, necessitating treatment with aggressive immunosuppressing agents. Unfortunately, his condition was further complicated by cytomegalovirus (CMV) pneumonia with respiratory failure. Standard antiviral agents, ganciclovir and CMV-intravenous immunoglobulin, were given. However, his pneumonia soon deteriorated into ARDS with progressively decreasing oxygenation. He began to have pulmonary hemorrhage with profuse blood-tinged secretions via the endotracheal tube. The bleeding was thought to be due to serious pulmonary damage from ARDS. Meanwhile, platelet count was kept at 53,000/μL, PT at 9.8 seconds, and aPTT at 25.6 seconds. The oxygenation was further compromised with a drop in oxygen saturation (SaO_2) to 80% even on the maximum setting of the ventilator.

In an attempt to save his life, one dose of rFVIIa 80 μg/kg was tried immediately. Soon after the injection of rFVIIa, bleeding from the endotracheal tube subsided and his SaO_2 went up dramatically to 92% 30 minutes later. The SaO_2 stayed above 95% for an additional 12 hours, accompanied by a decrease in the secretion of blood-tinged sputum. Unfortunately, his SaO_2 dropped again down to 80%. Although not much blood-tinged secretion was in evidence this time, a second dose of rFVIIa 100 μg/kg was tried, but had no effect this time. The patient passed away because of severe pulmonary damage from ARDS.

3.3. Case 3

A 94-year-old woman with a history of chronic renal insufficiency for 9 years was noted to have massive tarry-bloody stool passage, which caused hypovolemic shock. Aggressive transfusion of blood components was immediately provided and a thorough endoscopic study to search for any bleeder in the gastrointestinal tract was recommended. However, her family refused any invasive procedure including endoscopy or angiography because of her advanced age. Initial laboratory data showed WBC 13,600/μL, hemoglobin 6.4 g/dL, platelet count 245,000/μL, PT 10.7 seconds, aPTT 24.2 seconds, blood urea nitrogen 55 mg/dL, and creatinine 4.9 mg/dL. In addition to blood components transfusion including whole blood, packed red cells and fresh frozen plasma, tranexamic acid and desmopressin were given to help control bleeding as well. However, the bleeding persisted with blood pressure dropping to 77/52 mmHg, hemoglobin to 5.9 g/dL, and platelet count to 78,000/μL, while PT went up to 24.1 seconds and aPTT to 47.8 seconds. Furthermore, pulmonary edema developed due to volume overload after aggressive transfusion. So, one dose of rFVIIa in a 100 μg/kg intravenous bolus injection was tried. Dramatically, her bleeding stopped 2 hours later, with PT down to 8.4 seconds and aPTT to 31.5 seconds. However, tarry-bloody stool passage recurred 24 hours later. As her family continued to refuse endoscopic or angiographic studies, repeated doses of rFVIIa 100 μg/kg were given at intervals of 2–4 hours. The gastrointestinal bleeding finally stopped after administration of an additional six doses of rFVIIa. Her hemodynamics stabilized with no more tarry stool passage. Unfortunately, acute myocardial infarction occurred 15 hours after the last dose of rFVIIa. Although no more bleeding was found thereafter, she passed away due to cardiogenic shock.

3.4. Case 4

A 46-year-old man diagnosed with oral squamous cell carcinoma with metastases affecting multiple bones and the left axillary lymph node had received a course of systemic chemotherapy of cisplatin plus 96-hour 5-fluorouracil infusion. Although the tumor shrank, 18 days later, his condition was complicated by an episode of massive bloody stool passage which immediately put him into hypovolemic shock. Both esophagogastroduodenoscopy and colonoscopy disclosed no causative bleeder. Laboratory data showed WBC 11,400/μL, hemoglobin 7.5 g/dL, platelet count 83,000/μL, PT 13.1 seconds and aPTT 43.7 seconds. The prolongation of aPTT was probably due to loss of plasma proteins from bleeding, since his baseline PT and aPTT were in the normal range.

Transfusion with multiple blood components was initially provided, and his aPTT returned to within normal limits. The bleeding recurred the next day. Angiography was performed but no bleeder was found. Once again, massive bloody stool was noted on the third day. Angiography was immediately performed, showing hyperemic distribution of blood vessels originating from the superior mesenteric artery, but still a definite bleeder could not be identified. Because no coagulopathy was found in this patient, two doses of rFVIIa 85 μg/kg were administrated at 2-hour intervals. The initial response was good, stabilizing hemodynamics and no further bloody passage was seen. Unfortunately, 4 hours after the first dose of rFVIIa, massive bleeding recurred. The third angiography disclosed two active bleeders on the branches of the superior mesenteric artery. Embolization was performed smoothly, stopping the hemorrhage. However, sudden onset of bleeding occurred again the next day, which caused a standstill, and it was too late to perform any invasive hemostatic procedure.

4. Discussion

We report a series of four patients who were treated with rFVIIa for uncontrolled, life-threatening hemorrhage in the absence of an inherited bleeding disorder. The clinical responses varied. Sustained and effective hemostasis was achieved in one patient. Two patients showed a partially effective response and the last patient did not respond to treatment. Although rFVIIa has shown excellent hemostatic effects for treating bleeding in hemophilia with inhibitors, its role as a universal hemostatic agent remains debatable and experience using rFVIIa outside of the hemophilia population are somewhat limited. Numerous case reports have been published in the past [10–14]. All four patients had bleeding that could not be stopped initially by medical treatment, including massive transfusion of blood components, use of antifibrinolytic agents and even repeated surgery to ligate the bleeding vessels. Hemostasis was successfully achieved by injection of rFVIIa 90 μg/kg of variable doses. Subsequently, several retrospective studies including more patients have been published. For example, O'Connell et al reported that in a study with a total of 40 patients who received rFVIIa for uncontrolled bleeding from different causes, bleeding stopped or decreased in 80% [15]. Other reports described potential response for upper gastrointestinal bleeding [16], postvascular surgery [17] and postpartum hemorrhage [18].

To date, several randomized clinical trials using rFVIIa for non-hemophilic bleeding have been completed. In 36 patients who underwent retropubic prostatectomy, Friederich et al reported that a single preoperative dose of rFVIIa, either 20 μg/kg or 40 μg/kg, reduced blood loss by 50–60% [19]. Mayer et al conducted a randomized trial of 399 patients with spontaneous intracerebral hemorrhage that showed significant reduction in the growth of hematoma, mortality and improved functional outcomes for the rFVIIa treatment groups (receiving one dose of rFVIIa 40 μg/kg, one dose of 80 μg/kg or one dose of 160 μg/kg *vs.* placebo) [20]. Significant reduction in need for blood components transfusion has also been noted in treatment for blunt or penetrating traumatic hemorrhage after using rFVIIa as an adjuvant therapy [21]. In contrast, in 245 patients with liver cirrhosis and either variceal or non-variceal upper gastrointestinal bleeding, Bosch et al failed to show better hemostasis in the rFVIIa treatment group [22], but the study did reveal some improvement in the control of variceal bleeding in patients with Child-Pugh B and C liver function.

Moreover, rFVIIa may also help control bleeding in patients with thrombocytopenia. It is well known that platelets play an important role in hemostasis, both in the formation of the primary hemostatic platelet plug and through generation of procoagulant activity, leading to stabilization of the plug by fibrin. The latter effect is especially augmented by rFVIIa, since rFVIIa can activate platelets and recruit greater numbers of activated platelets to the site of vascular injury than would normally occur in thrombocytopenia [7,8]. In one study, 74 patients with thrombocytopenia were infused with rFVIIa [23]. A reduction in bleeding time occurred in 52% of evaluable treatment episodes. In another study, rFVIIa was used to manage hemorrhage in 24 patients with thrombocytopenia associated with hematologic malignancies. Bleeding stopped in 46% and markedly decreased in 33% of patients, respectively [24]. Our first patient with myelodysplastic syndrome and pneumonia whose condition was complicated by severe thrombocytopenia and gastrointestinal bleeding showed an excellent response of hemostasis after rFVIIa injection.

The optimal dosage of rFVIIa for the control of non-hemophilic bleeding remains to be established. Experience with hemophilic patients shows that to achieve maximum clinical hemostasis, the dosage of rFVIIa should be high enough to maintain a plasma level of factor VII activity (VII:C) of >600%, corresponding roughly to a dose of 90–120 μg/kg [25]. Currently, in patients with hemophilia A or B with inhibitors and acquired hemophilia, the recommended dosage of rFVIIa is 90 μg/kg at intervals of 2–3 hours [26]. Most published reports in the literature have applied a dosage range similar to that used for hemophilia [15,18,20,22–24], the majority using one to two doses. For massive traumatic hemorrhage, an Israeli group recommended an initial dosage of 120 μg/kg that may be followed by an additional dosage of 100 μg/kg [27]. It seems some patients have an excellent response to only one dose of rFVIIa but others may need more doses to control bleeding, as demonstrated by our cases. Although PT is universally shortened after a conventional single dose of rFVIIa, it remains an indirect measurement of thrombin generation and the shortening in PT may not reflect an adequate amount of thrombin production that allows clinical bleeding to continue. More recently, the application of clot waveform analysis and thrombin generation assays have provided more precise assessment of clotting function when monitoring rFVIIa treatment for hemophilia [28]. In addition, a higher dosage of rFVIIa may be needed for patients with inadequate thrombin generation in response to conventional dosage. Dosage up to 200 μg/kg have been tried in both hemophilic and non-hemophilic patients with good response [21,29]. However, the efficacy and safety of high-dose rFVIIa remains to be investigated in well-designed trials.

With over a decade of use, rFVIIa has generally been well tolerated by patients with hemophilia with inhibitors. Although serious adverse events, mainly thromboembolic effects, may occur in approximately 1% of patients [30], most of the thrombotic events occurred in patients with predisposing factors. However, in the trial using rFVIIa for acute intracerebral hemorrhage, Mayer et al demonstrated a trend toward more thromboembolic events than in the placebo group, 7% *vs.* 2% ($p=0.12$) [20]. In our series, Case 3 died of acute myocardial infarction after seven doses of rFVIIa injection, despite slowing intractable gastrointestinal bleeding. Her very advanced age and/or possible underlying atherosclerosis may have played a role in the development of myocardial infarction. However, the safety of rFVIIa for treating non-hemophilic patients, especially elderly ones, needs further clarification.

In conclusion, there is a clinical need for one or more new hemostatic agents to treat bleeding that cannot be controlled by surgical intervention, local hemostatic procedures, and transfusion of blood products. Based on our experience and previously reported series, rFVIIa may be used as a last attempt to stop life-threatening hemorrhage. However, clinical hemostatic effects that could not be translated into a survival benefit among our cases calls for further research, especially with regard to appropriate timing of its clinical use. Its wide use and safety concerns warrant further clinical study.

References

1. Hedner U, Glazer S, Pingel K, et al. Successful use of recombinant VIIa in patient with severe haemophilia A during synovectomy. *Lancet* 1988;2:1193.
2. Ingerslev J. Efficacy and safety of recombinant factor VIIa in the prophylaxis of bleeding in various surgical procedures in hemophilic patients with factor VIII and factor IX inhibitors. *Semin Throm Haemost* 2000;26: 425–32.
3. Lusher J, Ingerslev J, Roberts H, Hedner U. Clinical experience with recombinant factor VIIa. *Blood Coagul Fibrinolysis* 1998;9:119–28.
4. Baudo F, De Cataldo F, Gaidano G. Treatment of acquired factor VIII inhibitor with recombinant activated factor VIIa: data from the Italian registry of acquired hemophilia. *Haematologica* 2004;89:759–61.
5. Bauer KA. Treatment of factor VII deficiency with recombinant factor VIIa. *Haemostasis* 1996;26(Suppl 1): 155–8.
6. Poon MC, D'Oiron R, Von Depka M, et al. Prophylactic and therapeutic recombinant factor VIIa administration to patients with Glanzmann's thrombasthenia: results of an international survey. *J Thromb Haemost* 2004;2: 1096–103.
7. Hoffman M. A cell-based model of coagulation and the role of factor VIIa. *Blood Rev* 2003;17(Suppl 1):S1–5.
8. Roberts HR, Monroe DM, Oliver JA, Chang JY, Hoffman M. Newer concepts of blood coagulation. *Haemophilia* 1998; 4:331–4.
9. Hedner U. NovoSeven as a universal haemostatic agent. *Blood Coagul Fibrinolysis* 2000;11(Suppl 1):S107–11.
10. Bernstein D. Effectiveness of the recombinant factor VIIa in patients with the coagulopathy of advanced Child's B and C cirrhosis. *Semin Thromb Hemost* 2000;26: 437–8.
11. Hendriks HG, van der Maaten JM, de Wolf J, Waterbolk TW, Slooff MJ, van der Meer J. An effective treatment of severe intractable bleeding after valve repair by one single dose of activated recombinant factor VII. *Anesth Analg* 2001;93:287–9.
12. Moscardo F, Perez F, de la Rubia J, et al. Successful treatment of severe intra-abdominal bleeding associated with disseminated intravascular coagulation using recombinant activated factor VII. *Br J Haematol* 2001;114: 174–6.
13. Vlot AJ, Ton E, Mackaay AJ, Kramer MH, Gaillard CA. Treatment of a severely bleeding patient without preexisting coagulopathy with activated recombinant factor VII. *Am J Med* 2000;108:421–3.
14. White B, McHale J, Ravi N, et al. Successful use of recombinant FVIIa (Novoseven) in the management of intractable

post-surgical intra-abdominal haemorrhage. *Br J Haematol* 1999;107:677–8.
15. O'Connell NM, Perry DJ, Hodgson AJ, O'Shaughnessy DF, Laffan MA, Smith OP. Recombinant FVIIa in the management of uncontrolled hemorrhage. *Transfusion* 2003;43: 1711–6.
16. Vilstrup H, Markiewicz M, Biesma D, et al. Recombinant activated factor VII in an unselected series of cases with upper gastrointestinal bleeding. *Thromb Res* 2006;118: 595–601.
17. Manning BJ, Hynes N, Courtney DF, Sultan S. Recombinant factor VIIa in the treatment of intractable bleeding in vascular surgery. *Eur J Vasc Endovasc Surg* 2005;30:525–7.
18. Ahonen J, Jokela R. Recombinant factor VIIa for life-threatening post-partum haemorrhage. *Br J Anaesth* 2005; 94:592–5.
19. Friederich PW, Henny CP, Messelink EJ, et al. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomized trial. *Lancet* 2003;361:201–5.
20. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005;352:777–85.
21. Rizoli SB, Chughtai T. The emerging role of recombinant activated factor VII (rFVIIa) in the treatment of blunt traumatic haemorrhage. *Expert Opin Biol Ther* 2006;6: 73–81.
22. Bosch J, Thabut D, Bendtsen F, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. *Gastroenterology* 2004;127:1123–30.
23. Kristensen J, Killander A, Hippe E, et al. Clinical experience with recombinant factor VIIa in patients with thrombocytopenia. *Haemostasis* 1996;26(Suppl 1):159–64.
24. Brenner B, Hoffman R, Balashov D, Shutluko E, Culic SD, Nizamoutdinova E. Control of bleeding caused by thrombocytopenia associated with hematologic malignancy: an audit of the clinical use of recombinant activated factor VII. *Clin Appl Thromb/Hemost* 2005;11:401–10.
25. Hedner U. Dosing and monitoring NovoSeven treatment. *Haemostasis* 1996;26(Suppl 1):102–8.
26. Siddiqui MA, Scott LJ. Recombinant factor VIIa (Eptacog Alfa): a review of its use in congenital or acquired haemophilia and other congenital bleeding disorders. *Drugs* 2005; 65:1161–77.
27. Martinowitz U, Michaelson M. Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force. *J Thromb Haemost* 2005;3:640–8.
28. Matsumoto T, Shima M, Takeyama M, et al. The measurement of low levels of factor VIII or factor IX in hemophilia A and hemophilia B plasma by clot waveform analysis and thrombin generation assay. *J Thromb Haemost* 2006;4: 377–84.
29. Parameswaran R, Shapiro AD, Gill JC, Kessler CM. Dose effect and efficacy of rFVIIa in the treatment of haemophilia patients with inhibitors: analysis from the Hemophilia and Thrombosis Research Society Registry. *Haemophilia* 2005;11:100–6.
30. Abshire T, Kenet G. Recombinant factor VIIa: review of efficacy, dosing regimens and safety in patients with congenital and acquired factor VIII or IX inhibitors. *J Thromb Haemost* 2004;2:899–909.