

# Recombinant factor VIIa for patients with inhibitors to factor VIII or IX or factor VII deficiency

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**Summary.** Inhibitors to factor VIII (FVIII) or IX (FIX) in patients with haemophilia A or B create a challenging problem for the treatment of these patients. Recombinant FVIIa (rFVIIa; NovoSeven<sup>®</sup>, Novo Nordisk A/S, Bagsvaerd, Denmark) is a realistic treatment option, owing to its specific mode of action and lack of immunogenicity.

This was a multicentre, open-label, compassionate-use trial in patients with severe haemophilia A (FVIII:C < 1%) or B (FIX:C < 1%) with inhibitors, acquired antibodies to FVIII or FIX, or FVII deficiency (FVII:C < 5%), for whom alternative therapies had failed or were contraindicated. Patients received rFVIIa treatment for life- or limb-threatening bleeding episodes or for coverage during essential surgery. The mean rFVIIa dose was approximately 90 µg kg<sup>-1</sup> for haemophilia A/B and acquired inhibitor patients, and 25 µg kg<sup>-1</sup> for FVII-deficient patients. Efficacy data for 67 treatment episodes (45 bleeding episodes, 22 surgical procedures) are presented; seven patients were treated for a concurrent serious bleeding episode and surgical procedure. At the end of treatment,

rFVIIa was effective or partially effective in 85% of serious bleeding episodes. During surgery, bleeding was assessed as none or less than or equivalent to normal in 91% of surgical procedures; postoperatively, 91% of procedures were associated with no or minimal oozing.

During 60 separate treatment episodes, 26 adverse events (22 nonserious, four serious) were reported in 15 patients, during 17 bleeding episodes or surgical procedures. Only 10 were considered as having a possible, probable, or unknown relationship with rFVIIa; of these, fever ( $n=2$ ) and thrombophlebitis ( $n=3$ ) were the most common. There was no evidence of disseminated intravascular coagulation.

In conclusion, rFVIIa is an effective, well-tolerated treatment for serious bleeding episodes and bleeding associated with surgical procedures in patients with severe haemophilia A/B with inhibitors, acquired inhibitors, or FVII deficiency.

**Keywords:** haemophilia, inhibitors, factor VII deficiency, rFVIIa, surgery, bleeding episodes.

Haemophilia A/B, the acquisition of factor VIII (FVIII) or IX (FIX) inhibitors (in haemophilia and nonhaemophilia patients), and FVII deficiency are conditions associated with severe and life-threatening bleeding episodes. It is estimated that about 15% of the haemophiliac population have inhibitors to FVIII or FIX [1]. The acquisition of inhibitors is one of the most challenging problems associated with the treatment of haemophilia.

Therapeutic options that have been used to date include: overwhelming the inhibitors with large

doses of FVIII [2, 3]; the use of activated and nonactivated prothrombin complex concentrates (aPCC/PCC) and porcine FVIII [4–7]; induction of immune tolerance [2]; and plasmapheresis with or without absorption of antibody. These treatments all have potential disadvantages, including development of antiporcine antibodies in response to porcine FVIII, unpredictability of response, the possibility of transmission of blood-derived infections, high cost, and thromboembolic complications.

Recombinant FVIIa (rFVIIa; NovoSeven<sup>®</sup>, Novo Nordisk A/S, Bagsvaerd, Denmark) is an effective haemostatic agent that enhances the natural coagulation pathway and represents a significant advance in the management of patients with FVIII or FIX inhibitors. Owing to its unique mode of action, rFVIIa does not induce generalized coagulation [8, 9].

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It has also been shown to be nonimmunogenic in haemophilia A/B patients or in patients with acquired inhibitors [10]. Since rFVIIa is a recombinant product, there is no risk of the transfer of human viruses [11]. However, bovine serum proteins are used in its manufacture.

High haemostatic efficacy rates have been achieved with rFVIIa irrespective of the type of bleeding episode. Clinical trial results [9] and preliminary data from the Compassionate Use Programme have evaluated ear-nose-throat [12], central nervous system [13], retroperitoneal and gastrointestinal [14], muscle and joint [15], and various soft tissue bleeding episodes. Recombinant FVIIa has been used successfully during major surgical procedures, such as joint replacement and synovectomy [16], and minor procedures, such as central line insertion [17]. Compassionate-use treatment with rFVIIa, for acute bleeding episodes and during surgery, has been effective in approximately 80% of cases [18]. Doses of 60–120  $\mu\text{g kg}^{-1}$  rFVIIa every 2–3 h are recommended for these indications [19].

Cumulative data with rFVIIa, including both the Compassionate Use Programme and controlled clinical trials, now comprise 503 patients and 2438 bleeding episodes [20]. These data indicate that rFVIIa is well tolerated and suitable for treatment of patients with inhibitors [20].

The study reported here is part of the world-wide Compassionate Use Programme. The aim of this open-label, multicentre study was to evaluate the efficacy and safety of rFVIIa treatment for life- or limb-threatening bleeding episodes, or coverage during essential surgery, in patients with haemophilia A/B with inhibitors, acquired inhibitors, or FVII deficiency.

## Patients and methods

This was an open-label, compassionate-use trial conducted in 17 German centres between 10 November 1994 and 28 February 1996. Patients were eligible for treatment if they had severe haemophilia A (FVIII:C < 1%) or B (FIX:C < 1%) with inhibitors, acquired antibodies to FVIII or FIX, or FVII deficiency (FVII:C < 5%), and alternative therapies had failed or were contraindicated. Written informed consent was obtained from patients prior to therapy. Patients were considered to be at an increased risk of an adverse event, such as a thrombotic event or disseminated intravascular coagulation, if they had the following conditions: clinically active angina pectoris or evidence of advanced atherosclerotic

disease, septicaemia, hepatic failure, crush-injury, malignancy, or pregnancy.

Patients with haemophilia A/B and inhibitors, or acquired inhibitors were treated with rFVIIa for life- or limb-threatening bleeding episodes or for coverage during essential surgery. Treatment regimens varied. For acute bleeding episodes, patients received 90  $\mu\text{g kg}^{-1}$  rFVIIa (i.v. bolus) every 2 h until clinical improvement; increases to 120  $\mu\text{g kg}^{-1}$  were permitted if no clinical improvement was seen. In the case of controlled bleeding meriting continued treatment, the dosing interval could be increased to 3 h for 1–2 days, and subsequently to 4, 6, 8, or 12 h as long as treatment was indicated. For surgical procedures, patients received 90  $\mu\text{g kg}^{-1}$  rFVIIa (i.v. bolus) immediately prior to surgery, repeated at 2–3 h intervals for the subsequent 24–48 h. For major surgery, dosing could be continued at 2–4 h intervals for 6–7 days, increasing to 6–8 h for a further 2 weeks. Factor VII-deficient patients received 15–30  $\mu\text{g kg}^{-1}$  every 4–6 h for bleeding episodes or surgery. Re-bleeding was defined as bleeding occurring at the same site 24 h after having achieved haemostasis and was considered as a separate bleeding episode.

For serious bleeding episodes, clinical evaluation of the cause and type of bleed took place prior to the first injection of rFVIIa. Clinical response was then assessed 8 h and 24 h after the first injection and at the end of therapy. Efficacy was rated as effective (bleeding clinically significant and substantially reduced), partially effective (bleeding decreased somewhat), or ineffective (no improvement) compared with the pretreatment assessment.

For surgical procedures, the surgeon qualitatively estimated the amount of blood lost during surgery in comparison with healthy, nonhaemophilic patients as either none, less than normal, equivalent to normal, or greater than normal. The requirements for postoperative blood replacement were also taken into account. Post-operatively, bleeding complications were assessed as not observed, absent, minimal oozing, overt, or frank bleeding.

All adverse events were reported irrespective of severity, or whether or not the event was considered to be treatment related. Severe adverse events were any event considered to be fatal, life-threatening, permanently disabling, requiring in-patient hospitalization, congenital abnormalities, cancer, or overdose. All other adverse events were considered nonserious. Adverse events were classified as mild, moderate, or severe, and the relationship between the study drug and each adverse event was assessed by

the physician as being probable, possible, unlikely, unknown, or unrelated.

When multiple doses of rFVIIa were administered, prothrombin time and activated partial thromboplastin time were assessed. In addition, one of the following was monitored: fibrinogen, platelets, thrombin-antithrombin complex, D-dimer, fibrinopeptide A, fibrin-degradation products, fibrin monomer, antithrombin III, or  $\alpha_2$ -antiplasmin. Results from these tests were only collected if considered necessary by the investigator and if an adverse event had occurred.

All data were analysed descriptively. Patient characteristics, such as age and gender, and background variables, such as cause, site, and duration of bleeding, and type of surgery, were summarized. Efficacy data were evaluated by primary diagnosis.

## Results

A total of 28 patients aged between 1 and 70 years were treated (Table 1). Of these, 19 had haemophilia A/B with inhibitors, four had acquired inhibitors to FVIII, and five had FVII deficiency. Five patients were considered to be at an increased risk of

experiencing an adverse event due to pregnancy ( $n=1$ ), septicaemia ( $n=2$ ), or malignancy ( $n=2$ ). The majority of patients had received prior therapy with blood products, such as FVIII and aPCC/PCC, and two patients had previously received rFVIIa.

Sixty treatment episodes were recorded. However, seven patients were treated for both a serious bleeding episode and a surgical procedure simultaneously, so efficacy data are presented for 67 treatment episodes; 45 serious bleeding episodes and 22 surgical procedures. The majority of patients ( $n=15$ ) experienced only one bleeding episode. Of the patients treated for concurrent serious bleeding episode and surgery: one experienced a bleeding episode because of a leg fracture and underwent major orthopaedic surgery for reposition of the fracture; one suffered bleeding due to a gastric ulcer and underwent major GI surgery; one experienced bleeding due to untreated haemophilia A and underwent minor dental surgery; bleeding episodes were spontaneous in three patients and of unknown origin in one patient.

The mean treatment duration was  $8.1 \pm 7.6$  days (range 1–39 days) and the mean number of injections per treatment episode was  $43.2 \pm 35.4$  (range 1–142 injections). The mean number of injections for serious bleeding episodes and both major and minor surgical procedures by diagnostic category are given in Table 2. The mean number of injections per patient was 93.6 (range 9–371 injections). The mean dose was approximately  $90 \mu\text{g kg}^{-1}$  for haemophilia A/B and acquired inhibitor patients, and  $25 \mu\text{g kg}^{-1}$  for FVII-deficient patients. For serious bleeding episodes for which the information was available

**Table 1.** Patient demographics and characteristics.

	Number of patients ( $n=28$ )
<b>Primary diagnosis</b>	
Haemophilia A/B with inhibitors	19 (68%)
Acquired inhibitors	4 (14%)
FVII deficient	5 (18%)
<b>Gender</b>	
Male	25
Female	3
<b>Age (years)</b>	
0–5	4
6–16	12
17–59	9
>60	3
<b>Hepatitis status</b>	
Hepatitis B	5
Hepatitis C	11
<b>Therapy prior to rFVIIa treatment</b>	
FVIII	7 (25%)
Porcine FVIII	2 (7%)
aPCC/PCC	7 (25%)
Fresh frozen plasma	1 (4%)
Antifibrinolytics	6 (21%)
Cytostatics	1 (4%)
Corticosteroids	2 (7%)
Previous rFVIIa use	2 (7%)

**Table 2.** Details of number of injections for serious bleeding episodes, major and minor surgical procedures.

Treatment episode	Mean number of injections
<b>Serious bleeding episodes</b>	
Haemophilia A/B with inhibitor patients	46.8
Acquired inhibitor patients	42.2
FVII deficiency patients	53.1
<b>Surgical procedures</b>	
<i>Major procedures</i>	
Haemophilia A/B with inhibitor patients	75.0
Acquired inhibitor patients	81.2
FVII deficiency patients	89.0
<i>Minor procedures</i>	
Haemophilia A/B with inhibitor patients	114.0
Acquired inhibitor patients	67.7
FVII deficiency patients	37.1
Haemophilia A/B with inhibitor patients	34.1
Acquired inhibitor patients	113
FVII deficiency patients	5.0

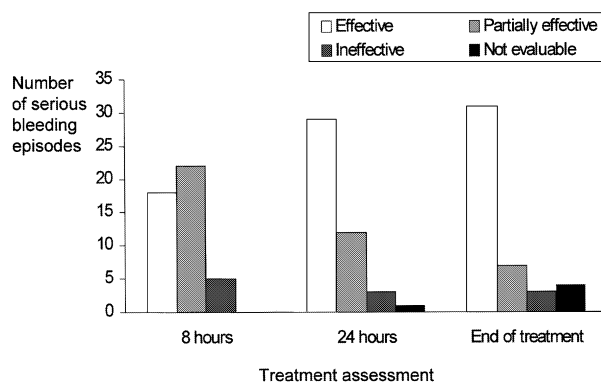


Fig. 1. Efficacy outcomes for serious bleeding episodes at 8 h, 24 h, and end of treatment. The majority of bleeding episodes were joint bleeds (23; 51%); other sites included abdominal cavity (four; 9%), CNS (two; 4%), muscle (two; 4%), retroperitoneal (two; 4%), dental (two; 4%), and ENT (one; 2%). The remainder (nine; 20%) were mucosal, soft tissue, and genitourinary bleeds.

( $n = 25$ ), the mean delay between the estimated onset of bleeding and the first rFVIIa dose was 23 h (range 0.5–122.0 h).

A total of 45 serious bleeding episodes were treated in 23 patients, the majority of which were joint bleeds (23; 51%). Efficacy outcomes at 8 h and 24 h and at the end of treatment are shown in Fig. 1. At treatment end, 31 cases (69%) were recorded as effective and seven (16%) as partially effective. Bleeding was stopped in less than 8 h in nine (20%), in 8–24 h in seven (16%), in 24–72 h in two (4%), and in more than 72 h in two (4%) episodes; in 25 episodes (56%) time to cessation was either not applicable (ineffective episodes) or was not recorded.

Therapy was ineffective at treatment end in three serious bleeding episodes: a spontaneous, severe knee-joint bleed; an abdominal cavity bleed of unknown cause; and a severe gastrointestinal bleed. The patient suffering the severe knee-joint bleed was a 9-year-old male with haemophilia A with inhibitors who relapsed 3 years after successful induction of immune tolerance. rFVIIa was used since other treatments (FVIII) had been ineffective in treating this bleeding episode and previous episodes had not been adequately controlled by other therapies, also previous treatment had led to an increased antibody titre. The patient with an abdominal cavity bleed was a 52-year-old male with acquired antibodies to FVIII. Treatment with rFVIIa was partially effective when assessed after 8 and 24 h; however, rFVIIa was stopped as it was later deemed to be ineffective, no other treatment was started. A rise in antibody titre had occurred in this patient during the treatment of other bleeding episodes and was expected when using other therapies. During a previous abdominal cavity bleed treatment with FIX concentrate, desmopressin and aprotinin was ineffective; however, treatment with FVIII concentrate had been effective. The patient who suffered the severe gastrointestinal bleed experienced a 'decreased therapeutic response' adverse event; details are given below.

Twenty-two surgical procedures were performed in 17 patients. During surgery, bleeding was assessed as none or less than or equivalent to normal in all minor and 60% of major surgical procedures (Table 3). Post-operative bleeding was assessed as not observed or absent or minimal oozing in 88% of

Table 3. Efficacy assessment by surgical procedure.

Surgery	<i>n</i>	Assessment of blood loss during surgery			Postoperative assessment of bleeding		
		None	Less than normal or equivalent to normal	More than normal	Not visible or none	Minimal oozing	Frank or overt bleeding
<b>Major</b>							
CNS	1	0	1	0	1	0	0
GI	2	0	0	2	1	1	0
Orthopaedic	2*	1	1	0	2	0	0
Total major	5	1 (20%)	2 (40%)	2 (40%)	4 (80%)	1 (20%)	0 (0%)
<b>Minor</b>							
Central line placement	9	2	7	0	7	1	1
Wound revision	2	0	2	0	0	1	1
Synovectomy	1	1	0	0	1	0	0
Dental	1	0	1	0	1	0	0
Other	4	0	4	0	3	1	0
Total minor	17	3 (18%)	14 (82%)	0 (0%)	12 (70%)	3 (18%)	2 (12%)
Total	22	4 (18%)	16 (73%)	2 (9%)	16 (73%)	4 (18%)	2 (9%)

\* One patient underwent two procedures: reposition of a fracture and extension of the right leg, and subsequent surgery for the removal of the metal used for the extension.

**Table 4.** Adverse events which had a possible, probable, or unknown relationship with rFVIIa.

	Number of adverse events (%)
Fever	2
Pain	1
Therapeutic response decreased	1
Haemorrhage (not otherwise specified)	1
Thrombophlebitis	3
Nausea	1
Vomiting	1
Total (% of treatment episodes)	10 (17%)

minor and all major procedures (Table 3). Postoperative transfusion was required in two major (GI) and two minor (wound) procedures.

Four of the five FVII-deficient patients were treated for four serious bleeding episodes. In these patients, treatment was effective in two episodes and partially effective in two episodes. The responses at 8 h, 24 h, and at the end of treatment were identical in each patient. Three FVII-deficient patients underwent four surgical procedures. During surgery, there was no bleeding during one procedure and a normal amount of bleeding in three procedures. No postoperative bleeding was observed in all four cases.

During 60 separate treatment episodes, 26 adverse events (22 nonserious, four serious) were reported in 15 patients during 17 bleeding episodes or surgical procedures. Ten adverse events were considered as having a possible, probable, or unknown relationship with rFVIIa administration (Table 4); the most common being fever ( $n=2$ ) and thrombophlebitis ( $n=3$ ), which was reported in two patients being treated for a serious bleeding episode. These two patients had no apparent risk factors for thrombophlebitis. There were no adverse events that prompted collection of coagulation test results.

The four serious adverse events that were reported in four patients included decreased therapeutic response to rFVIIa, intracranial hypertension, intracranial haemorrhage, and haemorrhage (not otherwise specified). Of these, only one event (decreased therapeutic response) was considered as possibly related to treatment and represents a treatment failure as opposed to an actual adverse event. This 38-year-old male, haemophilia A patient was admitted to hospital due to a severe upper gastrointestinal bleed treated with FVIII inhibitor bypass activity (FEIBA) complex. Seven days later the patient underwent gastrointestinal surgery (Billroth-II-resection) for gastrointestinal bleeding, and haemostasis

was achieved with rFVIIa treatment. Twelve hours post-operation, the patient suffered a rupture of a subcapsular haematoma of the spleen, probably due to surgical rupture during operation (although therapeutic failure cannot be excluded). Strong bleeding continued during subsequent surgery to remove the spleen. Recombinant FVIIa treatment was ceased and the patient was stabilized on aPCC and FVIII. Seven days later, rFVIIa treatment was reinitiated for uncontrollable abdominal bleeding which started after an acute, deep, explosive cough. Therapeutic response to rFVIIa decreased and the patient died following the development of peritonitis sepsis and multiple organ failure.

The patient who experienced intracranial haemorrhage was a 22-year-old man who had haemophilia A with inhibitors. He was admitted to hospital with a staphylococcal infection. Five days later, he experienced haemothorax and was treated with rFVIIa; he also required artificial respiration for more than a week. The patient developed intracranial bleeding 8 days after rFVIIa started. However, coagulation had been improved by rFVIIa therapy. This patient died during treatment, but the death was considered to be unrelated to rFVIIa treatment.

In the FVII-deficient patient population, there were three adverse events in three patients. Of these only one (intracranial hypertension) in a 64-year-old man was considered to be serious, and this event, which resulted in death, was considered as unlikely to be related to rFVIIa.

One FVII-deficient patient was found to have a transient low-titre antibody against rFVIIa when assayed 3 months after treatment with rFVIIa. He had, however, been given plasma-derived FVII before rFVIIa and the antibodies may have been induced by one or both of these FVII products. The patient's antibodies had disappeared at a follow-up examination 4 months later.

## Discussion

The results from this study demonstrate that rFVIIa is a safe and effective treatment for patients with haemophilia A/B, acquired inhibitors, or FVII deficiency. Recombinant FVIIa treatment was effective or partially effective in 85% of serious bleeding episodes at the end of treatment. This is comparable or superior to results found with other agents, such as aPCC/PCC [21–26]. Treatment with rFVIIa was also effective for coverage during surgery; blood loss was assessed as none or less than or equivalent to normal in 91% of surgical procedures and postoperative

assessments showed that 91% of procedures were associated with no or minimal oozing.

This study demonstrates that low-dose rFVIIa (15–30 µg kg<sup>-1</sup>) is effective in the treatment of bleeding episodes or for coverage during surgery in FVII-deficient patients. This confirms earlier results showing the efficacy of single, low doses of rFVIIa [27].

Recombinant FVIIa was found to have very few side-effects. Only one serious adverse event was considered possibly related to treatment, a patient who died from refractory bleeding. This most likely represents a treatment failure in a patient with multiple major bleeding sites, including a ruptured spleen. The adverse event profile did not indicate any trend towards increased risk of thrombogenicity and there was no evidence of a generalized activation of the coagulation cascade, confirming results from several other studies [8, 9].

The efficacy rates reported here were in patients who received treatment as a last resort, having failed other treatments. Studies of first line rFVIIa treatment have reported higher efficacy rates: in the home setting, haemostasis was achieved in 92% of patients with mild or moderate bleeding episodes [28], and in surgery, efficacy rates of 97% have been reported [29]. In first line treatment, the mean number of injections required to attain haemostasis is also considerably reduced [28, 30].

In conclusion, rFVIIa is effective and well tolerated in the treatment of serious bleeding episodes and bleeding associated with surgical procedures in patients with severe haemophilia with inhibitors, acquired inhibitors, and FVII-deficient patients. Treatment is associated with very few side-effects and a minimal risk of thrombogenicity or disseminated intravascular coagulation.

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