

Congenital factor VII deficiency: therapy with recombinant activated factor VII – a critical appraisal

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Summary. Congenital factor VII (FVII) deficiency is a rare bleeding disorder with high phenotypic variability, and optimal management has yet to be determined. Treatment has traditionally involved FVII replacement therapy using fresh frozen plasma, prothrombin complex concentrates or plasma-derived FVII concentrates. Recombinant activated FVII (rFVIIa, NovoSeven®), the first recombinant treatment option, has recently been approved in the European Union for use in congenital FVII deficiency, but has been available on an emergency and compassionate use basis since 1988. In FVII deficiency, rFVIIa serves as substitution therapy as it provides the physiological ligand (FVIIa) for tissue factor, its receptor exposed at the site of vascular injury. This paper provides an overview of published and unpublished experience with rFVIIa in patients with congenital FVII deficiency from the NovoSeven compassionate and emergency use programmes (1988–99) and of independent reports in the litera-

ture. Recombinant FVIIa has been reported to provide effective haemostasis in patients of all ages and in a range of bleeding situations, including acute central nervous system/life-threatening bleeding episodes (15 episodes in 12 patients), non-life-threatening bleeding episodes (>32 episodes in 17 patients), surgery (>40 interventions in 25 patients) and childbirth (three women). Preliminary reports suggest that it may also be effective prophylactically. The risk of thrombosis in FVII-deficient patients treated with rFVIIa is unknown, as is the occurrence of inhibiting antibodies. A postlicensure pharmacovigilance registry (Seven Treatment Evaluation Registry) has been set up to continue to monitor the efficacy and safety (including alloantibody development) of rFVIIa in patients with FVII deficiency.

Keywords: bleeding disorder, congenital factor VII deficiency, NovoSeven, recombinant factor VIIa, substitution therapy

Introduction

Congenital factor VII (FVII) deficiency is a rare bleeding disorder affecting both males and females [1]. It is characterized by increased bleeding after surgery and trauma in mildly affected individuals, and by spontaneous, severe and even life-threatening bleeding in those severely affected [1–4]. Correlation between factor VII coagulation activity (FVII:C) and bleeding tendency appears to be poor [1]. However, severe bleeding episodes tend to occur most often in

homozygous or compound heterozygous individuals with FVII:C levels <2% of normal [5–8]. Haemostasis can generally be achieved by raising FVII:C levels above 10–15% of normal [9]. Activated FVII (FVIIa) is thought to be the initiator of blood coagulation through the classic extrinsic pathway; its physiological levels, although very low (about 1% of the total FVII mass, i.e. 10–100 pM), are essential to create the binary complex with tissue factor where and when this receptor becomes available at the site of vascular injury, which leads to localized coagulation [10,11].

Factor VII replacement has traditionally been achieved with fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs) or plasma-derived FVII concentrates [12]. However, plasma-derived products are associated with a risk of transmission of pathogens. In addition, the use of PCCs results in an unwanted increase in other vitamin-K-dependent

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factors and is associated with both arterial and venous thrombosis [13–15]. Intravenous administration of recombinant FVIIa (rFVIIa, NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark) is now widely used for the treatment of FVII deficiency, but no clear cut information on dosages and treatment schedules are available [9,16–19]. Initially approved for use in haemophilia with inhibitors, rFVIIa has recently received approval in the European Union to treat bleeding in patients with congenital FVII deficiency or patients with Glanzmann's thrombasthenia who are refractory to platelet transfusions. The rationale behind the use of rFVIIa in congenital FVII deficiency is based on the fact that it provides only the missing protein in a low-volume preparation, and is devoid of other human proteins and potential blood-borne pathogens.

This paper reviews experience with rFVIIa in patients with congenital FVII deficiency from the NovoSeven compassionate and emergency use programmes (1988–99) and from independent published reports.

Independent publications

Independent published reports of FVII-deficient patients treated with rFVIIa, without any other concurrent source of FVII, were identified from the results of a cross-database (BIOSIS, Current Contents, EMBASE, MEDLINE) literature search for the period from 1 January 1995 to 1 February 2003. One of the retrieved abstracts was later updated by a publication, and this latter publication has been used as the citation [7]. An abstract presented at the Novo Nordisk Symposium on Treatment of Bleeding and

Thrombotic Disorders, Copenhagen 2001, has also been included [20]. In addition, a recently published report of three cases is discussed [21].

Independent published reports, 1 January 1995 to 1 February 2003

Independent reports have described the use of rFVIIa in 20 patients with congenital FVII deficiency in 26 treatment episodes (Table 1).

Surgery under cover of rFVIIa was the most frequent reason for using rFVIIa (Fig. 1), and all reported cases were completed without excessive bleeding. A 6-h dosing interval for patients undergoing surgery was supported by preoperative pharmacokinetic and pharmacodynamic assessments of rFVIIa administered at $20 \mu\text{g kg}^{-1}$ in two patients (see Table 2) [9]. Treatment of acute bleeding episodes included one case of severe menorrhagia and three infants with gastrointestinal bleeding and/or intracranial haemorrhage (ICH) [22–25]. These episodes were resolved satisfactorily and without drug-related complications. The successful use of rFVIIa has also been reported in two Caesarean sections and one vaginal birth in patients with congenital FVII deficiency [17,26,27].

Other reports have described the use of rFVIIa in children as prophylaxis for ICH, recurrent epistaxis, menorrhagia and haemarthrosis [7,20,23,24,28,29]. The dosing regimens were in the range of $15\text{--}90 \mu\text{g kg}^{-1}$ by bolus injection from twice daily to twice weekly for up to 2 years. All regimens resulted in a reduced number of spontaneous bleeds or an absence of bleeding problems, although no information was reported on the severity of observed bleeds for which prophylaxis was instituted.

Table 1. Independent published reports (1 January 1995 to 1 February 2003) – treatment episodes and recombinant activated factor VII (rFVIIa) exposure.

Treatment episode	No. of treatment episodes (no. of patients*)	Age range (years)	rFVIIa dosing regimen	Reference
Cover during surgery	11 (8)	13–85	$11\text{--}40 \mu\text{g kg}^{-1}$, then $11\text{--}20 \mu\text{g kg}^{-1}$ every 5–8 h by bolus injection or $2.5 \mu\text{g kg}^{-1} \text{h}^{-1}$ by continuous infusion	[9,16,22,30–33]
Acute bleeding	5 (4)	0–55	10 or $25\text{--}80 \mu\text{g kg}^{-1}$, then $15\text{--}30 \mu\text{g kg}^{-1}$ every 4–12 h by bolus injection; or $2.5 \mu\text{g kg}^{-1}$, then $5 \mu\text{g kg}^{-1} \text{h}^{-1}$ by continuous infusion, with $2.5 \mu\text{g kg}^{-1}$ every 4 h	[22–25]
Childbirth and Caesarean section	3 (3)	22–30	$20\text{--}50 \mu\text{g kg}^{-1}$, then $10\text{--}35 \mu\text{g kg}^{-1}$ every 4–6 h by bolus injection; or $13 \mu\text{g kg}^{-1}$, then $1.7\text{--}3.3 \mu\text{g kg}^{-1} \text{h}^{-1}$ by continuous infusion	[17,26,27]
Long-term prophylactic use (≥ 5 months)	7 (7)	0–15	$15\text{--}90 \mu\text{g kg}^{-1}$ from twice daily to twice weekly by bolus injection	[7,20,23,24,28,29]

*Some patients received rFVIIa for more than one treatment episode.

Fig. 1. Reasons for recombinant activated factor VII (FVII) use in independent published reports of congenital FVII deficiency (1 January 1995 to 1 February 2003).

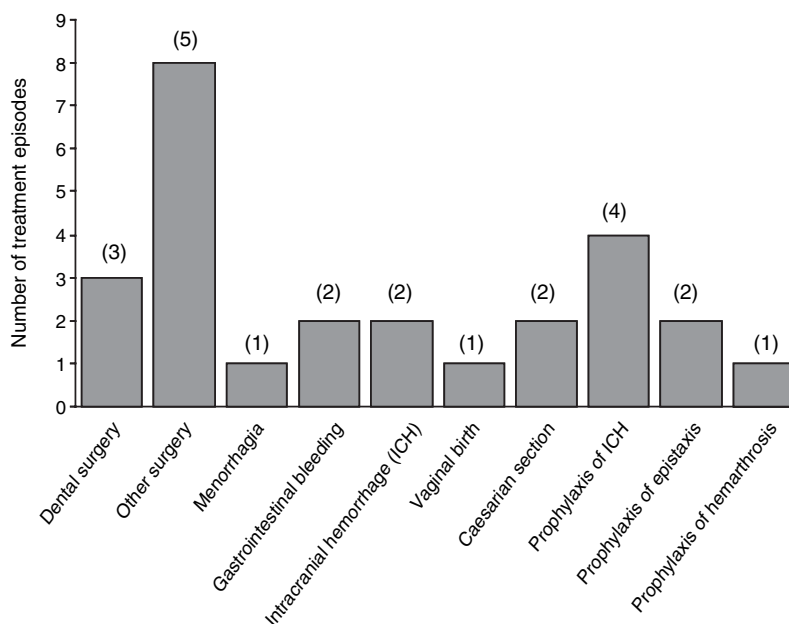


Table 2. Factor VII (FVII) coagulation activity (FVII:C) and prothrombin time (PT), before and after dosing with recombinant activated FVII (rFVIIa) $20 \mu\text{g kg}^{-1}$, in severe FVII-deficient patients undergoing surgery.

Before dosing		10 min after rFVIIa		6 h after rFVIIa	
FVII:C (%)*	PT (s)	FVII:C (%)*	PT (s)	FVII:C (%)*	PT (s)
Patient 1					
<1	29	430–670 ($n = 8$)	7–9	30–62 ($n = 8$)	9–15
Patient 2					
<1	28	700–830 ($n = 2$)	10	46–82 ($n = 2$)	12

*Percentage of normal level.

Source from Ingerslev *et al.* [9].

A transient normalization of prothrombin time (PT) was seen in all episodes that reported PT measurements. The only adverse event (AE) related to rFVIIa was mild localized phlebitis at the site of administration during continuous infusion in a woman undergoing Caesarean section [27]. There were no thromboembolic complications. There was no evidence of FVII alloantibody development in the episodes of long-term prophylactic use. However, a spontaneous report to Novo Nordisk has revealed that one of the surgical patients developed FVII alloantibodies after using a total dose of 161 mg of rFVIIa over 6 years [34]. The patient had also been exposed to PCCs.

Report of Mathijssen *et al.* [21]

This report describes the use of rFVIIa in three adult patients with congenital FVII deficiency who had previously received plasma-derived products. Two women aged 17 and 28 years had a severe bleeding tendency and received rFVIIa prophylactically at a dosage of $17.6\text{--}19.0 \mu\text{g kg}^{-1}$ two to three times

weekly. In both cases, the frequency and severity of bleeding decreased compared with that observed previously with plasma-derived FVII. The third patient was a 35-year-old man who received rFVIIa on demand. He reported fewer small bleeding episodes after beginning rFVIIa therapy, and also underwent several surgical procedures (e.g. extraction of wisdom teeth and surgery of the vocal cords) under protection with rFVIIa and tranexamic acid without excessive bleeding.

Compassionate and emergency use programmes

Recombinant FVIIa has been available on a compassionate and emergency use basis since 1988 for patients with haemophilia with inhibitors to FVIII or FIX, non-haemophilia patients with autoantibodies to FVIII or FIX, and patients with congenital FVII deficiency. The compassionate and emergency use programmes permitted open-label use of rFVIIa for acute treatment of life-threatening haemorrhage or maintenance of haemostasis during surgery, when no alternative treatment was available or where other

Table 3. Compassionate and emergency use programmes – patient characteristics ($n = 32$) and type of treatment episode.

Characteristic	No. of patients (%)	
Gender		
Female	12 (38)	
Male	20 (62)	
Ethnic origin		
African-American	4 (13)	
Caucasian	9 (28)	
Oriental	1 (3)	
Other	6 (19)	
Unknown	12 (38)	
Age groups (years)		
0–5	8 (25)	
6–16	7 (21)	
17–59	14 (43)	
60–81	3 (9)	
Type of treatment episode	No. of patients	No. of episodes
Surgical	16	26
Acute bleeding		
Joint bleeds	5	20
CNS bleeds	7	8
Life-limb threatening/CNS	3	6
Internal bleeds	1	2
Muscle	1	1
Other	6	6

complications, such as risk of thromboembolism (based on age, cardiovascular risk, etc.), could be foreseen. Physicians were requested to record details of haemostatic response and AEs. Several publications have reported experiences from the compassionate and emergency use programmes [5,35–41].

Overview of FVII deficiency cases from the compassionate and emergency use programmes

Demographic and other baseline characteristics of the 32 FVII-deficient patients included in the programmes between 1988 and 1999 are summarized in Table 3. The inclusion criteria specified a FVII:C level of <5% of normal. A total of 69 treatment episodes included 43 non-surgical bleeds and 26 surgery-related treatments. The number of treatment episodes per patient varied; the highest number of treatment episodes was 18 over a 14-month period for a 4-year-old boy.

Dose regimens varied, with single or multiple doses being used depending on the clinical setting. The median dose per injection ($22 \mu\text{g kg}^{-1}$) was within the dose range recommended in the protocols for FVII-deficient patients ($15\text{--}30 \mu\text{g kg}^{-1}$ every 4–6 h until haemostasis was achieved). The median dose per injection was similar for the different types of bleeding episodes *per se* and when classified as mild/moderate and severe bleedings (Table 4). As a large number of severe bleeding episodes required only a single injection of rFVIIa, the median total dose per treatment episode was low for severe bleedings. However, more severe bleedings [e.g. central nervous system (CNS) and internal bleeding episodes] were treated for a longer period of time.

Treatment with rFVIIa was rated as effective in 37 of 43 (86%) of non-surgical bleeding episodes and in all surgical procedures for which data were collected (25/26, 96%; see Table 5). Efficacy of rFVIIa in

Table 4. Compassionate and emergency use programmes – exposure to rFVIIa.

	Bleeding severity*			Total
	Severe	Mild/moderate	Other	
No. of treatment episodes	31	30	6	67†
Average dose per injection per treatment episode ($\mu\text{g kg}^{-1}$)				
Median	21	21	31	22
Range	6–98	9–91	22–85	6–98
Total dose per treatment episode (mg kg^{-1})				
Median	0.035	0.324	1.087	0.300
Range	0.018–4.800	0.009–2.945	0.420–2.258	0.009–4.800
Treatment duration (days)				
Median	0	2.6	5.5	2.3
Range	0–50.8	0–13.9	2–28	0–50.8
Total no. of injections				
Median	1	10	35	10
Range	1–124	1–112	13–102	1–124
Mean no. of injections per day				
Median	4	4	5	4
Range	1–8	1–13	3–7	1–13

*Bleeding episodes were classified as severe (CNS, life- and limb-threatening/CNS, internal bleedings, recurrent joint bleedings), mild/moderate (surgery, single joint bleedings, muscle bleedings) or other (other and unknown).

†Two patients were treated for both an acute bleeding and a surgical procedure during the same treatment episode.

Table 5. Compassionate and emergency use programmes – efficacy of recombinant activated factor VII (rFVIIa) in patients with congenital FVII deficiency.

	Surgery	Non-surgical bleeding episodes			Total
		CNS	Joint	Other*	
Effective	25	11	20	6	62
Partially effective	0	2	0	1	3
Ineffective	0	1	0	0	1
Other†	0	0	0	2	2
Data not collected	1	0	0	0	1
Total	26	14	20	9	69
Effective (%)	25/26 (96)	37/43 (86)			62/69 (90)

CNS, CNS and life-limb threatening/CNS.

*Other represents muscle and internal bleeding episodes as well as 'other'.

†For two patients, outcome was reported only as 'died'. For one of these patients, outcome of the rFVIIa treatment was later reported as successful by the investigator. Outcome of rFVIIa treatment for both patients was therefore listed as 'other'.

non-surgical bleedings appeared to be independent of the location of the bleed.

Treatment with rFVIIa was partially effective in a 64-year-old man with an intracranial haematoma. In haemostatic terms, treatment was effective, but did not result in neurological improvement. Another case of partially effective treatment was a 12-year-old girl with hypermenorrhagia. After initiation of treatment with rFVIIa, blood loss decreased, but despite co-administration of tranexamic acid, blood loss increased on day 8 of treatment. The third case of partially effective treatment was a 15-year-old girl with acute lymphoid leukaemia, who underwent bone marrow transplantation, and who received rFVIIa for 6 days for a pulmonary bleeding. Although PT was corrected, pulmonary bleeding continued. Treatment was rated as ineffective in a man who had a craniotomy successfully performed under cover of rFVIIa, but who was later readmitted with a large extradural haemorrhage. A craniotomy with evacuation of a clot was performed under rFVIIa cover, but the patient's clinical condition deteriorated. Cause of death was a massive extradural haemorrhage; this case was a failed response to rFVIIa.

A total of 28 AEs were reported by 13 (41%) patients. No thromboembolic complications were reported in the examined programmes/case reports. Most non-serious AEs were single, diverse events and were of mild or moderate severity. One non-serious AE (intracranial hypertension) in a 43-year-old male surgical patient was considered possibly related to rFVIIa, but treatment was continued and the patient recovered completely. Ten serious adverse events (SAEs) were reported in nine (28%) patients, inclu-

ding viral infection, transplant rejection and/or sepsis, antibody against FVII, intracranial/extradural haemorrhage, respiratory insufficiency, cardiac arrest and intracranial hypertension. All nine patients died as the result of a severe underlying clinical condition; none of the deaths was considered to be related to treatment with rFVIIa.

Antibodies against FVII developed in two of 13 patients evaluated for antibody formation [39,42]. One case was a 7-month-old girl who, by mistake, received a rFVIIa dosage of 800 µg kg⁻¹ (body weight 3 kg; total dose 4.8 mg kg⁻¹) on the first day of a treatment episode. There were no thrombotic complications and the treatment was rated as effective. Subsequent treatment with rFVIIa was at the recommended dose. This patient was one of the nine patients experiencing an SAE; fatal ICH occurred 4 months after the last rFVIIa dose. In the second case, FVII alloantibodies were detected 3 months after a single rFVIIa treatment episode in a 4-year-old boy. In the latter case, clinical response to rFVIIa was excellent, and the antibody was transient and most likely not inhibitory (F. Bergmann, personal communication). Both patients had previously been treated with plasma-derived FVII.

Discussion

The treatment episodes reviewed here are likely to represent only a proportion of the cases in which rFVIIa has been used off-label in patients with FVII deficiency. As successful treatment is more likely to be reported than failed treatment, there is the potential for positive bias in the independent published reports. However, with rFVIIa now licensed in the European Union for use in congenital FVII deficiency, the knowledge base in FVII-deficient patients is set to increase.

In the compassionate and emergency use programmes, the amount of data collected was limited. However, the available data provide convincing evidence of the efficacy of rFVIIa in both children and adults with FVII deficiency. Recombinant FVIIa was effective or partially effective in 65 of 69 (94%) of the treatment episodes; efficacy or partial efficacy rates ranged from 93% for CNS bleeds to 100% for surgical episodes and joint bleeds. Evaluation of efficacy can be problematic when variable criteria are used for assessment as in these cases. However, these efficacy rates are similar to those observed for another substitution therapy – rFVIII in patients with haemophilia – for which efficacy rates of 76–100% have been reported [43–46]. Patients with FVII deficiency in the compassionate and emergency

use programmes were generally treated with rFVIIa after failure of other therapy.

Dose regimens have varied in patients with FVII deficiency and this is a serious drawback for the efficacy evaluation. However, in general, the recommended dose of 15–30 $\mu\text{g kg}^{-1}$ rFVIIa every 4–6 h, which is based on the results of a clinical study [5], appears to be effective in maintaining haemostasis during bleeding episodes or surgery. In the compassionate and emergency use programmes, partially effective and ineffective outcomes were only observed in non-surgical bleeding situations. Two of the four cases were CNS bleedings, and all episodes appeared to have been complicated.

The most likely concerns that physicians may have in considering the use of rFVIIa in patients with FVII deficiency relate to the risks of thrombosis and the development of inhibitory antibodies. Apparently spontaneous thromboembolic events have been reported in patients with FVII deficiency who have not been undergoing treatment [14]. In addition, thromboembolic episodes have been reported in surgical patients with FVII deficiency [14]. Surgery is a well-known and powerful triggering factor for thrombosis, and replacement therapies (FFP, PCCs or plasma-derived FVII concentrates) may contribute to the problem by providing unnecessarily high levels of FVII and also other activated and non-activated factors (FIX/FIXa, FX/FXa and FIIa). This latter point suggests that replacement therapy should ideally be carried out using a pure FVII concentrate in controlled dosages. An accurate analysis of the literature (11 cases) and of nine previously unreported cases with FVII deficiency and thrombosis showed that no episode was related to the use of rFVIIa [14]. A subsequently referred case of FVII deficiency and thrombosis was also unrelated to the use of rFVIIa. Despite high FVII:C levels observed immediately after infusion of rFVIIa (see Table 2), no thromboembolic complications have been reported with the use of rFVIIa in the compassionate and emergency use programmes or in the literature. However, three thromboembolic events in FVII-deficient patients who received rFVIIa were spontaneously reported to Novo Nordisk before rFVIIa was approved for use in FVII deficiency (two arterial thrombotic events and one pulmonary embolism). It is not known if these patients had severe FVII deficiency, and at least two of the cases involved doses of rFVIIa that were higher than the recommended dose (one case, 90 $\mu\text{g kg}^{-1}$ followed by 40 $\mu\text{g kg}^{-1}$; second case, two doses of 50 $\mu\text{g kg}^{-1}$).

Very recently, a comparative analysis of thromboembolic events in patients given factor VIII inhibitor

bypass activity or rFVIIa, collected as part of the MedWatch programme of the US Food and Drug Administration, has been published [15]. However, the data included in this report are insufficient as no information is reported on the clinical settings or the treatment schedules used, and so trauma patients are compared with haemophiliacs or patients with other congenital or acquired haemorrhagic disorders [15,47].

At present there are too few data to draw any conclusions, and the risk of thrombosis in FVII-deficient patients treated with rFVIIa remains unknown. Until further data become available, the risk of thrombosis should be taken into account in evaluating the need and the dose of substitution therapy, especially for patients undergoing surgery.

There has been no systematic testing for FVII alloantibody development in patients with FVII deficiency receiving rFVIIa. To date, three instances of FVII alloantibody development have been identified in patients with FVII deficiency treated with rFVIIa. One case was described in an independent published report, and two cases were from the compassionate and emergency use programmes in which 13 patients were tested for antibody formation [34,39,42]. All three patients had previously been exposed to plasma-derived FVII, and therefore it remains uncertain as to whether or not rFVIIa was the cause of the alloantibody formation. In addition, little is known about the kinetic features of these alloantibodies. At present there are insufficient data on substitution therapy in FVII deficiency to draw any conclusions regarding the risk of clinically significant alloantibody formation.

Factor VII deficiency requires substitution therapy with only relatively small amounts of rFVIIa. The recommended dose of 15–30 $\mu\text{g kg}^{-1}$ every 4–6 h is considerably less than the dose generally used in patients with haemophilia (90 $\mu\text{g kg}^{-1}$ every 2–3 h until haemostasis). This may be explained by the fact that, unlike the situation in patients with haemophilia, FVII-deficient patients have an intact FXI-feedback loop ensuring appropriate amplification of initial thrombin generation [48]. The pharmacokinetic profile of rFVIIa in patients with FVII deficiency also differs from that in the adult haemophilia and normal populations [49]. In patients with FVII deficiency, clearance is faster, with an associated increase in the volume of distribution and lower recovery, than in patients with haemophilia, healthy volunteers on oral anticoagulants and patients with non-bleeding cirrhosis. This observation could be explained by the presence of free vascular binding sites for rFVIIa, which are fully or partially occupied

in individuals with normal levels of endogenous FVII.

In summary, rFVIIa is now being used for the treatment of clinically significant bleeding in patients with congenital FVII deficiency. Recombinant FVIIa appears to provide effective haemostasis in a range of bleeding situations, and preliminary reports suggest that it may also be effective in prophylactic use. The risk of thrombosis in FVII-deficient patients treated with rFVIIa is currently unknown. Therefore, the initiative of the Study Group of the International Registry on Factor VII Deficiency (IRF7) (For further information gmariani@cc.univaq.it or assister@targetseven.org), in collaboration with Novo Nordisk, to establish a postmarketing data collection system – the Seven Treatment Evaluation Registry (STER) – is certainly welcome. This registry will prospectively collect efficacy and safety data, including incidences of thrombosis and inhibitory antibody formation, on all kinds of treatment of patients with FVII deficiency. In this study, alloantibody assessment will be performed in a centralized fashion, as will plasma recovery of FVII after replacement therapy. These data will provide additional information to aid clinicians in the management of FVII deficiency in the future.

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Conflict of interest statement

GM is co-ordinator of the IRF7 (International Registry on F7) Study Group; the Group, since the year 2000 has been receiving an unrestricted Grant from Novo Nordisk to implement the research activities. GM, also has participated in a number of meetings organized by Novo Nordisk. JI is a member of the IRF7 and has contributed at various meetings organized by Novo Nordisk. BAK is an investigator in clinical trials and has served as a consultant for NovoNordisk.

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