

This article was downloaded by:[Novo Nordisk A/S]  
On: 26 July 2007  
Access Details: [subscription number 769981938]  
Publisher: Informa Healthcare  
Informa Ltd Registered in England and Wales Registered Number: 1072954  
Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



## Hematology

Publication details, including instructions for authors and subscription information:  
<http://www.informaworld.com/smpp/title~content=t713643071>

### Experience with recombinant-activated factor VII in 30 patients with congenital factor VII deficiency

Online Publication Date: 01 February 2007

To cite this Article: Brenner, Benjamin and Wiis, Jørgen (2007) 'Experience with recombinant-activated factor VII in 30 patients with congenital factor VII deficiency', *Hematology*, 12:1, 55 - 62

To link to this article: DOI: 10.1080/10245330601111573

URL: <http://dx.doi.org/10.1080/10245330601111573>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article maybe used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

© Taylor and Francis 2007

## Experience with recombinant-activated factor VII in 30 patients with congenital factor VII deficiency

BENJAMIN BRENNER<sup>1</sup> & JØRGEN WIIS<sup>2</sup>

<sup>1</sup>*Thrombosis and Hemostasis Unit, Department of Hematology and Bone Marrow Transplantation, Rambam Medical Center, Haifa, Israel, and* <sup>2</sup>*Intensive Care Unit 4131, National University Hospital, Copenhagen, Denmark*

(Received 6 August 2006; accepted 8 October 2006)

### Abstract

Recombinant-activated factor VII (rFVIIa) represents a therapeutic advance for the treatment and prevention of haemorrhage in patients with the rare bleeding disorder, congenital FVII deficiency. Thirty-nine cases of the use of rFVIIa in 30 patients with congenital FVII deficiency were identified from the international, internet-based registry *haemostasis.com*, which is a repository of case reports on the investigational use of rFVIIa that have been voluntarily submitted by physicians worldwide. These registry data have limitations compared with clinical-trial data but give valuable insights into a treatment for a rare disease that is virtually impossible to assess in conventional clinical trials. rFVIIa was used in: elective surgery (13 cases); haematoma (9 cases); emergency surgery (6 cases); epistaxis (4 cases); menorrhagia (2 cases); cover during childbirth (2 cases); disseminated intravascular coagulation (1 case; premature infant); removal of intradermal stitches (1 case); and haematuria (1 case). In 22/39 cases, rFVIIa was used prophylactically. Total dose and dosing schedules varied; median individual dose was 13.3 µg/kg body weight (bw) (range 1.2–223.8 µg/kg bw), median total dose was 38 µg/kg bw (range 1.2–758 µg/kg bw) and median number of doses was 3 (range 1–55). rFVIIa was generally associated with bleeding cessation or markedly reduced bleeding. Two adverse events were reported, but neither was regarded as being related to rFVIIa. These 39 cases support data confirming the safety and efficacy of rFVIIa in its EU-licensed indications, including that for preventing and/or controlling haemorrhage in patients with congenital FVII deficiency.

**Keywords:** *Congenital factor VII deficiency, haemorrhage, recombinant-activated factor VII, rFVIIa, replacement therapy*

### Introduction

Congenital factor VII (FVII) deficiency is a rare autosomal-recessive bleeding disorder that has an estimated incidence of 1/500,000 of the general population [1]. FVII plays a pivotal role in the initiation of haemostasis and coagulation. Binding of FVII to tissue factor (TF) in the damaged vascular bed results in rapid conversion of FVII to activated FVII (FVIIa) through the action of proteases [2]. In turn, FVIIa plays a key role in the early phases of the intrinsic and extrinsic pathways of coagulation through its activation of factor IX (FIX) and factor X (FX) [2]. Molecular studies have identified more than 40 single base-pair deletions and several short deletions in the FVII gene [3]. The clinical

consequences of these mutations vary [4]; a multi-centre study of 313 patients with congenital FVII deficiency identified 125 different mutations in the FVII gene; these mutations are associated with a range of clinical phenotypes, from asymptomatic to life-threatening and disabling disease states [5].

Type I FVII deficiency, which is characterised by low levels of both FVII activity and the FVII antigen (as opposed to type II deficiency, which is characterised by low levels of FVII activity but virtually normal FVII antigen levels), is the most common form of the disease and causes highly variable symptoms that correlate poorly with FVII levels [6–8]. However, data have shown that FVII activity of less than 1% is associated with a severe bleeding disorder that is

Correspondence: B. Brenner, Thrombosis and Hemostasis Unit, Department of Hematology and Bone Marrow Transplantation, Rambam Medical Center, P.O. Box 9602, Haifa 31096, Israel. Tel: 972 4 8542541. Fax: 972 4 515 710. E-mail: b\_brenner@rambam.health.gov.il

equivalent to severe FVIII deficiency [9]. The most frequent spontaneous symptoms of FVII deficiency include nosebleeds, menorrhagia, haemarthrosis and soft-tissue bleeding [7,10]. Severe and life-threatening intracranial bleeding is reported to occur in at least 16% of FVII-deficient neonates [11], but this complication has been observed only rarely in other case series [7,12].

Haemostasis can generally be achieved by raising FVII activity levels above 10–15% of normal levels [13]. Current treatment options rely mainly on replacement therapy [5,10] and include recombinant FVIIa (rFVIIa), plasma-derived FVII concentrates, prothrombin concentrates (PCCs), older FIX concentrates and fresh frozen plasma (FFP) [6,14,15]. Although older FIX concentrates have been used to treat FVII-deficient patients [16–18], these contain variable amounts of FVII, along with potentially thrombolytic, activated forms of FVII, FIX and FX [6,16]. In contrast, modern FIX concentrates, which are prepared using monoclonal antibodies and recombinant forms of FIX, contain no FVII and cannot be used to treat FVII deficiency [6]. Plasma infusions with FFP are associated with a risk of volume overload, infectious complications and an inability to reach the required levels of FVII activity, and are only recommended when other treatment options are unavailable [6,15,19].

Recombinant FVIIa (NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark) (15–30 µg/kg bw at 4–12 h intervals) is regarded as the treatment of choice for FVII deficiency [6,10,15,20,21]. It was originally developed for the treatment of bleeding in patients with haemophilia A or B with inhibitors towards FVIII or FIX, respectively. However, rFVIIa is increasingly being used as a haemostatic agent for the treatment of bleeding in a variety of conditions, such as Glanzmann's thrombasthaenia [22–26], von Willebrand disease [25–29], Bernard–Soulier syndrome [22,30–32] and FXI deficiency [33,34]. Accordingly, in February 2004, the European Medicines Agency (EMA) approved rFVIIa for the treatment of haemorrhage associated with congenital FVII deficiency and platelet-refractory Glanzmann's thrombasthaenia.

Although case reports of the use of rFVIIa in patients with congenital FVII deficiency have appeared in the literature [10,21,35–45], full-scale randomised clinical trials have not been possible due to the low frequency of the condition. In situations in which clinical trials are difficult to perform, voluntary registry submissions have provided valuable insight into the investigational use of drugs. *Haemostasis.com* is an international, internet-based registry that was established to capture clinical experiences relating to the investigational use of rFVIIa [46]. Between its launch in June 2001 and closure for data analysis in December 2003, more than 1100 entries covering a

range of indications have been recorded. We report here the findings of submissions to the *haemostasis.com* registry on the use of rFVIIa in congenital FVII deficiency.

## Materials and methods

### Patients

*Haemostasis.com* is a global web-based registry of case reports of patients treated with rFVIIa as prophylactic or rescue therapy for a diversity of severe bleeding episodes. The registry was independently managed and overseen by a steering committee of medical experts [46] and supported by an unrestricted educational grant from Novo Nordisk. Entry of records was voluntary and at the discretion of the case providers. In all cases, the rFVIIa had been purchased for its licensed indications by the case providers' institutions; no special provisions for supply were made. As no formal clinical investigation was undertaken and *haemostasis.com* served only as a repository, Ethical Committee approval was not sought.

Cases outlining the use of rFVIIa in patients with congenital FVII deficiency were identified from the *haemostasis.com* registry using the search term "Coagulopathy, congenital FVII deficiency". In order to minimise potential bias, all cases were included without pre-selection, regardless of whether or not data were available for all data categories.

Each bleeding episode, or case of bleeding prevention, was reported as a separate case, and cases were only included if (i) the case provider gave consent for their data to be published; and, (ii) sufficient data were available for meaningful analysis in the specific data category. A minimum amount of information had to be supplied by the case provider, who was asked to provide any data that were missing from the registry template and to validate the data that had already been entered in the case report.

### Data analysis

The registry template requested the following information from each case provider: patient age, gender, weight and blood pressure; cause, severity and site of bleeding; all medications administered before and after the use of rFVIIa, including antifibrinolytic therapy and haematological replacement therapy (number of units of blood products, e.g. packed cells, whole blood, FFP, cryoprecipitate, platelets; volume of crystalloids/colloids); dose of rFVIIa (µg/kg bw and total dose (in mg)), number of doses and interval between doses; response of bleeding to rFVIIa (classified as having "stopped", being "markedly decreased", "decreased", "unchanged" or "increased") and time to response; adverse events (AEs) or deaths and whether these were related to rFVIIa (classified as "probably or possibly

related”, “unlikely related” or “not related”); the results of any laboratory tests conducted, including coagulation parameters, such as international normalised ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT) and activated PTT (APTT), haemoglobin levels and platelet counts; patient outcome; and a brief case description. The records of the cases were then reviewed and case information was tabulated by the authors.

## Results

A total of 39 cases examining the use of rFVIIa in 30 patients with congenital FVII deficiency were identified from the *haemostasis.com* website. Four of the 30 patients were treated with rFVIIa on more than one occasion (three patients were admitted on three occasions and one patient was admitted on four occasions). Cases were submitted from physicians in the Czech Republic ( $n = 9$ ), UK ( $n = 8$ ), Denmark ( $n = 1$ ), Iraq ( $n = 9$ ) and Russia ( $n = 3$ ).

Table I provides the baseline patient and disease characteristics. Most patients were male (63%) and aged between 6 and 16 years old (47%). Of the 39 cases, 13 were admitted for elective surgery, nine for

bleeding associated with trauma (including five cases of haematoma and haemarthrosis and one case for correction of high INR); six for emergency surgery, four for epistaxis, two for menorrhagia, two for cover during childbirth, one for removal of intradermal stitches, one for disseminated intravascular coagulation (DIC) in a premature infant, and one for haematuria. In 22 of the 39 cases, rFVIIa was used prophylactically.

## Dosing

Overall, the median total dose of rFVIIa administered was 38  $\mu\text{g}/\text{kg}$  bw (range: 1.2–758  $\mu\text{g}/\text{kg}$  bw; data on total dose were unavailable for two patients). The median individual dose of rFVIIa was 13.3  $\mu\text{g}/\text{kg}$  bw (range: 1.2–223.8  $\mu\text{g}/\text{kg}$  bw; data on dose were unavailable for one case) and the median number of doses administered was 3 (range: 1–55; data on number of doses were unavailable for two patients). A total of 199 doses were administered, 89% of which were  $< 50$   $\mu\text{g}/\text{kg}$  bw. The median number of doses and total dose administered according to type of admission is shown in Table II. The dosing interval varied from 1 to 2–18 h. The highest total dose and highest number

Table I. Baseline patient and disease characteristics and reasons for recombinant-activated factor VIIa use in patients with congenital FVII deficiency ( $n = 30$  patients;  $n = 39$  cases).

Characteristic	Number of patients (%)	
Gender		
Female	10	(33)
Male	19	(63)
Not reported	1	(3)
Age group (years)		
0–5	5	(17)
6–16	14	(47)
17–59	8	(27)
60 +	2	(7)
Not reported	1	(3)
Weight (kg)		
0–25	10	(33)
26–50	6	(20)
51–75	11	(37)
76 +	3	(10)
FVII deficiency* (% of normal)		
0–10%	7	
11–35%	2	
Not reported	20	
Type of admission for rFVIIa use	Number of patients <sup>†</sup>	Number of cases
Elective surgery	12	13
Haematoma, haemarthrosis and/or trauma <sup>‡</sup>	6	9
Emergency surgery	6	6
Epistaxis	2	4
Menorrhagia	2	2
Cover during childbirth	2	2
Removal of intradermal stitches	1	1
Disseminated intravascular coagulation	1	1
Haematuria	1	1

\* In one case, FVII deficiency was reported as being “newly diagnosed”; <sup>†</sup> Individual cases could be categorised under more than one therapeutic area; <sup>‡</sup> Including one case for correction of high INR.

Table II. Dosing of recombinant-activated factor VIIa in patients with congenital factor VII deficiency ( $n = 30$  patients;  $n = 39$  cases).

Type of admission	Number of cases	Median number of doses (range)	Median total dose ( $\mu\text{g}/\text{kg}$ bw) (range)
Elective surgery	13	2.5 (1–55)	56.3 (24–758)
Haematoma, haemarthrosis and/or trauma	9	3 (1–7)	43.6 (2.4–656)
Emergency surgery	6	3 (1–4)	7.8 (4.8–51)
Epistaxis	4	1 (1)	1.2 (1.2)
Menorrhagia	2	4 (4)	7.2 (4.8–9.6)
Cover during birth	2*	4	191
Disseminated intravascular coagulation	1	3	447.6
Haematuria	1	4	4.8
Intradermal stitches	1	2	26.6

\*No data for one case.

of doses were administered to a woman with profuse bleeding from the liver that was not manageable by surgery and who was admitted on four separate occasions (total dose: 656, 58, 315 and 282.6  $\mu\text{g}/\text{kg}$  bw with 7, 1, 3 and 21 doses, respectively).

### Efficacy

In the absence of a quantitative assessment, case providers were requested to make a qualitative judgement of the effect of rFVIIa administration on blood loss, by categorising the overall effect of rFVIIa on haemorrhage. This information was available for 30/39 cases. Bleeding response to rFVIIa according to type of admission is shown in Table III.

In the 16/22 cases that reported bleeding response and used rFVIIa prophylactically, excessive bleeding was not reported. For the 9/13 cases of rFVIIa use for cover during elective surgery that reported bleeding response, there were no reports of excessive bleeding (Table III): in four cases, bleeding response was described as having “stopped”, in one case as being “markedly decreased”, in three cases as being “adequate to the procedure”, and in one case as being both “markedly decreased” and “adequate to the procedure”. In the 4/6 cases of emergency surgery that reported bleeding response, response to rFVIIa was assessed as having “stopped” in all four cases (Table III).

In the 8/9 reported cases of bleeding response associated with trauma, response to rFVIIa treatment was described as having “stopped” in four events and being “markedly decreased” in three events. Of these, four events (three described as having “stopped”; one described as being “markedly decreased”) corresponded to cases of haematoma and haemarthrosis. For the case with high INR, rFVIIa was administered prophylactically and no bleeding was reported.

In the 1/2 case of bleeding response for cover during birth, response to rFVIIa was described as having “stopped” in the case of an emergency Caesarean section (Table III). In all four cases of epistaxis,

bleeding response to rFVIIa treatment was assessed as having “stopped”. In the two individual events of haematuria and DIC, treatment response to rFVIIa was assessed as being “markedly reduced” and having “stopped”, respectively. In the two reported cases of menorrhagia, response to rFVIIa was described as being “markedly reduced” (Table III).

### Safety

AEs were reported in only two cases. In one case, in which rFVIIa was used as cover for elective surgery, AEs were described by the case provider as being: “thromboembolic events: epistaxis during febrile episode without association with surgery, FVII deficiency or therapy”; the patient had an outcome described as “excellent”. In the second case, which involved the use of rFVIIa during emergency surgery for a subarachnoid haemorrhage, a serious AE was described as “vasospasm, resulting in expressive dysphasia”. The physician involved considered the event unlikely to be related to rFVIIa administration. The final outcome for the patient was not recorded.

Two cases of bleeding-related mortality were reported in this series. One death occurred in a 25-year-old female, in whom rFVIIa was used as cover during labour. The other case was a 1-year-old male who was admitted for emergency surgery. Causality assessments in relation to the use of rFVIIa were not recorded for either case.

### Use of other medications

Information on the requirement for pre- and post-rFVIIa replacement therapy (including crystalloids/colloids) were reported in 11/39 cases. Of these, seven cases received blood-product replacement therapy during the 24 h before and/or after administration of rFVIIa (Table IV). Of the five cases that received blood-product replacement therapy in the 24 h before administration, three occurred in the same patient who suffered repeated liver trauma. Four of these five

Table III. Bleeding response to recombinant-activated factor VII in patients with congenital FVII deficiency.

Admission type	Total number of cases	Number of cases with data for bleeding response	Bleeding response to rFVIIa, number of cases*					Adequate for procedure <sup>†</sup>
			Stopped	Markedly decreased	Decreased	Not changed	Increased	
Elective surgery	13	9	4	2	—	—	—	4
Haematoma, haemarthrosis and/or trauma (including one patient with high INR)	9	8 <sup>‡</sup>	4	3	—	—	—	—
Emergency surgery	6	4	4	—	—	—	—	—
Epistaxis	4	4	4	—	—	—	—	—
Menorrhagia	2	2	—	2	—	—	—	—
Cover during birth	2	1	1	—	—	—	—	—
DIC	1	1	1	—	—	—	—	—
Haematuria	1	1	—	1	—	—	—	—
Intradermal stitches	1	0	—	—	—	—	—	—

DIC, disseminated intravascular coagulation; INR, International Normalised Ratio; \* Individual cases could be categorised under more than one bleeding response; <sup>†</sup> "Adequate response for procedure" was not included as one of the options for response to bleeding on the registry template but was reported using this wording for four cases; <sup>‡</sup> In the case of the high INR, rFVIIa was administered prophylactically and no bleeding was reported.

cases required additional replacement therapy in the 24 h following rFVIIa treatment. Two additional cases received replacement therapy in the 24 h following administration of rFVIIa; one case received two units of packed red blood cells following elective surgery and one case received additional blood products following treatment with rFVIIa to correct a high INR rather than to control bleeding.

Data on additional antifibrinolytic therapy were reported in 20/30 cases. Of these, additional anti-fibrinolytic therapy was administered to 12 patients: six received tranexamic acid; four received amino-methyl benzoic acid; and two received *para*-aminobenzoic acid. One patient who received *para*-aminobenzoic acid and three patients who received *para*-aminobenzoic acid were also administered etamsylate.

Antibiotics were commonly prescribed as additional therapy (14/39 cases). Other additional treatments included two patients who were treated with fibrin sealant (one of which was also treated with vasopressor drugs), and one patient who was treated with low-molecular-weight heparin. Glucocorticoids were administered to two patients (one with menorrhagia and one with haematuria).

## Discussion

The current study reviewed 39 cases in which rFVIIa has been used to treat or prevent bleeding episodes in a total of 30 patients with congenital FVII deficiency. These findings represent one of the largest single case series to date and provide convincing evidence for the use of rFVIIa as therapy for the treatment and prevention of bleeding in patients with FVII deficiency in a number of clinical settings, including controlling bleeding associated with elective and emergency surgery, parturition and trauma.

The data showed that, in most cases, a low median dose of rFVIIa (13.3 µg/kg bw) was effective in achieving haemostasis. Of the individual doses administered, 89% were less than 50 µg/kg bw. It has been hypothesised that lower doses of rFVIIa might be required to achieve effective haemostasis in patients with FVII deficiency due to the lower levels of FVII that are available to compete with FVIIa for binding to TF [47]. Our findings are consistent with this hypothesis and suggest that the recommended dosage of 15–30 µg/kg bw every 4–6 h for FVII deficiency (compared with 90 µg/kg bw for both haemophilia and Glanzmann's thrombasthaenia) is appropriate when treating bleeds associated with a deficiency in FVII.

The highest total dose and highest number of doses were administered to a woman who had profuse bleeding from the liver that was not manageable by surgery and was admitted on four separate occasions. The bleeding was caused by minor trauma and was markedly decreased by the use rFVIIa. Encouragingly,

Table IV. Blood products administered to patients with congenital factor VII deficiency in the 24 h before and after administration of recombinant-activated factor VII.

Case number*	Admission type	Blood products administered in 24 h before rFVIIa (units)	Blood products administered in 24 h after rFVIIa (units)
1	Elective surgery	None	2 (2 PRBCs)
11	DIC	28 (2 PRBCs + 8 whole blood, 16 FFP, 2 platelets)	1 (1 whole blood)
12	Liver trauma	28 (20 PRBCs + 8 FFP)	7 (5 FFP + 2 platelets)
13	Liver trauma	4 (4 PRBCs)	4 (4 FFP)
14	Liver trauma (to correct high INR)	None	4 (2 FFP + 2 platelets)
15	Liver trauma	4 (2 FFP and 2 platelets)	3 (1 FFP + 2 platelets)
34	Subarachnoid haemorrhage close to an aneurysm	5 (5 FFP)	None

Abbreviations: DIC = disseminated intravascular coagulation; FFP = fresh frozen plasma; INR = International Normalised Ratio; PRBCs = packed red blood cells; \* Cases 12–15 correspond to one patient who was admitted on four occasions.

the patient was reported to be alive after 1 year post-treatment, emphasising the potential clinical benefits of rFVIIa for patients with FVII deficiency. In general, the number of doses and total dose reflected the indication, with higher doses being used to prevent surgical bleeding and the lowest total doses controlling the four cases of spontaneous epistaxis.

Our findings are in agreement with previous case studies, the results of which have recently been summarised in a review by Mariani et al. [45]. The authors provided an overview of published and unpublished experience with rFVIIa in patients with congenital FVII deficiency, alongside the results of 32 patients from the NovoSeven compassionate and emergency use programmes (1988–1999). Collectively, these data showed that rFVIIa provides effective haemostasis in patients of all ages across 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 child birth (three women). In particular, a case report of the prophylactic use of rFVIIa for two patients with FVII deficiency undergoing elective surgery achieved excellent outcomes using low individual doses of 17–19 µg/kg bw rFVIIa that was administered every 6 h for up to 13 days [13]. Similarly, Mariani et al. [10] reported 17 patients with congenital FVII deficiency who were treated with rFVIIa for 27 spontaneous bleeding episodes in which the doses ranged from 8.1 to 70.5 µg/kg bw, concurring with the efficacy of low-dose rFVIIa that is shown in this *haemostasis.com* patient series.

Haemarthrosis is a common clinical indication of severe FVII deficiency [48]. Our series included five cases of haematoma and haemarthrosis, four of which were reported as having “stopped” and being “markedly reduced”. Bleeding was controlled by low total doses of rFVIIa. These findings are consistent

with the results of Mariani et al. [10], who reported that in many cases of haemarthrosis, single doses of 20 µg/kg bw were sufficient to prevent symptoms. These case study findings, together with the results reported in the current registry, are important in building the knowledge base for the use of rFVIIa for this rare bleeding disorder.

It is encouraging that the only two AEs reported by case providers in this series were not regarded by the physician as being related to rFVIIa administration. Two cases of bleeding-related mortality were also reported, although data were not available for the assessment of any likely relationship between the administration of rFVIIa and these outcomes. However, the safety of rFVIIa is supported by previous clinical experience with rFVIIa. Only two cases of DIC and 16 thrombotic events have been reported for >700,000 doses of 90 µg/kg bw rFVIIa that was administered for licensed indications between 1996 and 2003, suggesting that the lower dosage that is required for treating FVII deficiency will provide, at the least, comparable safety [49,50]. In addition, in the compassionate and emergency-use programmes reported by Mariani et al. [45], no thromboembolic complications were reported in the 32 patients examined and none of the nine deaths were considered to be related to treatment with rFVIIa.

The limitations of registry data, in comparison with that obtained from prospective, randomised clinical trials are recognised. These include the uncontrolled nature of a voluntary registry—physicians could decide whether or not to submit cases to the registry, which may have produced a bias towards the reporting of successful rather than unsuccessful data. In addition, some datasets were not complete for individual cases—to exclude any further potential bias, all cases were included in our analysis regardless of completeness. Finally, much of the data are qualitative and subjective, precluding robust statistical analysis. However, it is unlikely that there will be

sufficient appropriate candidates with FVII deficiency at any one time for a clinical trial to be feasible.

## Conclusion

Although these analyses are limited by the registry origin of the data, these safety findings, together with the evidence of efficacy, support previously published data of the use of rFVIIa to achieve haemostasis and prevent bleeding in patients with congenital FVII deficiency. Given the recent licensing of rFVIIa by the EMEA for the treatment of haemorrhage associated with congenital FVII deficiency and the difficulty of performing randomised controlled trials in this population, the registry provides valuable information on the use of rFVIIa in patients with congenital FVII deficiency in a “real-world” clinical setting.

## Acknowledgements

Case records published in this paper were obtained from the international, peer-reviewed, web-based registry, *haemostasis.com*. Case details were kindly provided by the following clinicians: Drs Baglin (UK), Bevan (UK), Blatný (Czech Republic), Bulikova (Czech Republic), Davies (UK), Forman (UK), Hassan (Iraq), Kahir (UK), Lee (UK), O’Shaughnessy (UK), Slechtova (Czech Republic) and Smejkal (Czech Republic). *Haemostasis.com* is supported by an unrestricted educational grant from Novo Nordisk.

## References

- [1] Hunault M, Bauer KA. Recombinant factor VIIa for the treatment of congenital factor VII deficiency. *Semin Thromb Hemost* 2000;26:401–405.
- [2] Hoffman M, Monroe DM, 3rd. A cell-based model of hemostasis. *Thromb Haemost* 2001;85:958–965.
- [3] Cooper DN, Millar DS, Wacey A, Banner DW, Tuddenham EG. Inherited factor VII deficiency: Molecular genetics and pathophysiology. *Thromb Haemost* 1997;78:151–160.
- [4] Herrmann FH, Wulff K, Auberger K, Aumann V, Bergmann F, Bergmann K, Bratanoff E, Franke D, Grundeis M, Kreuz W, Lenk H, Losonczy H, Maak B, Marx G, Mauz-Korholz C, Pollmann H, Serban M, Sutor A, Syrbe G, Vogel G, Weinstock N, Wenzel E, Wolf K. Molecular biology and clinical manifestation of hereditary factor VII deficiency. *Semin Thromb Hemost* 2000;26:393–400.
- [5] Mariani G, Herrmann FH, Dolce A, Batorova A, Etro D, Peyvandi F, Wulff K, Schved JF, Auerswald G, Ingerslev J, Bernardi F. International factor VII deficiency study group. Clinical phenotypes and factor VII genotype in congenital factor VII deficiency. *Thromb Haemost* 2005;93:481–487.
- [6] Bolton-Maggs PH, Perry DJ, Chalmers EA, Parapia LA, Wilde JT, Williams MD, Collins PW, Kitchen S, Dolan G, Mumford AD. The rare coagulation disorders—review with guidelines for management from the United Kingdom Haemophilia Centre Doctors’ Organisation. *Haemophilia* 2004;10:593–628.
- [7] Peyvandi F, Mannucci PM, Asti D, Abdoullahi M, Di Rocco N, Sharifian R. Clinical manifestations in 28 Italian and Iranian patients with severe factor VII deficiency. *Haemophilia* 1997;3:242–246.
- [8] Peyvandi F, Mannucci PM. Rare coagulation disorders. *Thromb Haemost* 1999;82:1207–1214.
- [9] Roberts HR, Lefkowitz JB. Inherited disorders of prothrombin conversion. 3rd ed. Philadelphia, USA: Lippincott JB; 1994. p 206–208.
- [10] Mariani G, Testa MG, Di Paolantonio T, Molskov Bech R, Hedner U. Use of recombinant, activated factor VII in the treatment of congenital factor VII deficiencies. *Vox Sanguinis* 1999;77:131–136.
- [11] Ragni MV, Lewis JH, Spero JA, Hasiba U. Factor VII deficiency. *Am J Hematol* 1981;10:79–88.
- [12] Acharya SS, Coughlin A, Dimichele DM. Rare bleeding disorder registry: Deficiencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias. *J Thromb Haemost* 2004;2:248–256.
- [13] Ingerslev J, Knudsen L, Hvid I, Tange MR, Fredberg U, Sneppen O. Use of recombinant factor VIIa in surgery in factor-VII-deficient patients. *Haemophilia* 1997;3:215–218.
- [14] Di Paola J, Nugent D, Young G. Current therapy for rare factor deficiencies. *Haemophilia* 2001;7(Suppl 1):16–22.
- [15] Mannucci PM, Duga S, Peyvandi F. Recessively inherited coagulation disorders. *Blood* 2004;104:1243–1252.
- [16] Ingerslev J, Kristensen HL. Clinical picture and treatment strategies in factor VII deficiency. *Haemophilia* 1998;4:689–696.
- [17] Kohler M, Hellstern P, Pindur G, Wenzel E, von Blohn G. Factor VII half-life after transfusion of a steam-treated prothrombin complex concentrate in a patient with homozygous factor VII deficiency. *Vox Sanguinis* 1989;56:200–201.
- [18] White GC, Lundblad RL, Kingdon HS. Prothrombin complex concentrates: Preparation, properties, and clinical uses. *Curr Topics Hematol* 1979;2:203–244.
- [19] Ramanarayanan J, Krishnan G, Hernandez-Ilizaliturri MD. Factor VII. eMedicine, Available from: <http://www.emedicine.com/med/topic3493.htm>. Accessed 28/01/05.
- [20] United Kingdom Haemophilia Centre Doctors’ Organisation. Guidelines on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. *Haemophilia* 2003;9:1–23.
- [21] Scharer I. Recombinant factor VIIa for patients with inhibitors to factor VIII or IX or factor VII deficiency. *Haemophilia* 1999;5:253–259.
- [22] Almeida AM, Khair K, Hann I, Liesner R. The use of recombinant factor VIIa in children with inherited platelet function disorders. *Br J Haematol* 2003;121:477–481.
- [23] Chuansumrit A, Sangkapreecha C, Hathirat P. Successful epistaxis control in a patient with Glanzmann thrombasthenia by increased bolus injection dose of recombinant factor VIIa. *Thromb Haemost* 1999;82:1778.
- [24] Poon MC, Demers C, Jobin F, Wu JW. Recombinant factor VIIa is effective for bleeding and surgery in patients with Glanzmann thrombasthenia. *Blood* 1999;94:3951–3953.
- [25] Poon MC, D’Oiron R, Von Depka M, Khair K, Negrier C, Karafoulidou A, Huth-Kuehne A, Morfini M. International data collection on recombinant factor VIIa and congenital platelet disorders study group. Prophylactic and therapeutic recombinant factor VIIa administration to patients with Glanzmann’s thrombasthenia: Results of an international survey. *J Thromb Haemost* 2004;2:1096–1103.
- [26] Tengborn L, Petruson B. A patient with Glanzmann thrombasthenia and epistaxis successfully treated with recombinant factor VIIa. *Thromb Haemost* 1996;75:981–982.
- [27] Ciavarella N, Schiavoni M, Valenzano E, Mangini F, Inchingolo F. Use of recombinant factor VIIa (NovoSeven) in the treatment of two patients with type III von Willebrand’s disease and an inhibitor against von Willebrand factor. *Haemostasis* 1996;26(Suppl 1):150–154.

- [28] Grossmann RE, Geisen U, Schwender S, Keller F. Continuous infusion of recombinant factor VIIa (NovoSeven) in the treatment of a patient with type III von Willebrand's disease and alloantibodies against von Willebrand factor. *Thromb Haemost* 2000;83:633–634.
- [29] Meijer K, Peters FT, van der Meer J. Recurrent severe bleeding from gastrointestinal angiodysplasia in a patient with von Willebrand's disease, controlled with recombinant factor VIIa. *Blood Coag Fibrinol* 2001;12:211–213.
- [30] Ozelo MC, Svirin P, Larina L. Use of recombinant factor VIIa in the management of severe bleeding episodes in patients with Bernard-Soulier syndrome. *Ann Hematol* 2005 July 26 Epub ahead of print.
- [31] Peters M, Heijboer H. Treatment of a patient with Bernard-Soulier syndrome and recurrent nosebleeds with recombinant factor VIIa. *Thromb Haemost* 1998;80:352.
- [32] Poon MC, d'Oiron R. Recombinant activated factor VII (NovoSeven) treatment of platelet-related bleeding disorders. International registry on recombinant factor VIIa and congenital platelet disorders group. *Blood Coag Fibrinol* 2000;11(Suppl 1):S55–S68.
- [33] Billon S, Le Niger C, Escoffre-Barbe M, Vicariot M, Abgrall JF. The use of recombinant factor VIIa (NovoSeven) in a patient with factor XI deficiency and a circulating anticoagulant. *Blood Coag Fibrinol* 2001;12:551–553.
- [34] Lawler P, White B, Pye S, Hermans C, Riddell A, Costello C, Brown S, Lee CA. Successful use of recombinant factor VIIa in a patient with inhibitor secondary to severe factor XI deficiency. *Haemophilia* 2002;8:145–148.
- [35] Billio A, Pescosta N, Rosanelli C, Amaddii G, Fontanella F, Coser P. Successful short-term oral surgery prophylaxis with rFVIIa in severe congenital factor VII deficiency. *Blood Coag Fibrinol* 1997;8:249–250.
- [36] Chuansumrit A, Visanuyothin N, Puapunwattana S, Chaivisuth A, Rasmidat P, Charoenkwan P, Chiemchanya S. Outcome of intracranial hemorrhage in infants with congenital factor VII deficiency. *J Med Assoc Thailand* 2002;85(Suppl 4):S1059–S1064.
- [37] Eskandari N, Feldman N, Greenspoon JS. Factor VII deficiency in pregnancy treated with recombinant factor VIIa. *Obst Gynecol* 2002;99:935–937.
- [38] Huang WY, Kruskall MS, Bauer KA, Uhl L, Shaz BH. The use of recombinant activated factor VII in three patients with central nervous system hemorrhages associated with factor VII deficiency. *Transfusion* 2004;44:1562–1566.
- [39] Maimon M, Bernstein T, Kenet G, Kapelushnik J. Recombinant factor VIIa for treatment of a child with severe factor VII deficiency and coarctation of the aorta. *J Pediatr Hematol/Oncol* 2003;25:591.
- [40] Mathijssen NC, Masereeuw R, Verbeek K, Lavergne JM, Costa JM, van Heerde WL, Novakova IR. Prophylactic effect of recombinant factor VIIa in factor VII deficient patients. *Br J Haematol* 2004;125:494–499.
- [41] Niikura T, Nishikawa T, Saegusa Y, Fujishiro T, Yoshiya S, Kurosaka M. Total hip arthroplasty in severe congenital factor VII deficiency: Successful use of recombinant activated factor VII for hemostasis. *J Arthroplast* 2005;20:396–400.
- [42] Tcheng WY, Donkin J, Konzal S, Wong WY. Recombinant factor VIIa prophylaxis in a patient with severe congenital factor VII deficiency. *Haemophilia* 2004;10:295–298.
- [43] White B, Martin M, Kelleher S, Browne P, McCann SR, Smith OP. Successful use of recombinant FVIIa (NovoSeven) in the management of pulmonary haemorrhage secondary to Aspergillus infection in a patient with leukaemia and acquired FVII deficiency. *Br J Haematol* 1999;106:254–255.
- [44] White B, O'Connor H, Smith OP. Successful use of recombinant VIIa (NovoSeven) and endometrial ablation in a patient with intractable menorrhagia secondary to FVII deficiency. *Blood Coag Fibrinol* 2000;11:155–157.
- [45] Mariani G, Konkle BA, Ingerslev J. Congenital factor VII deficiency: Therapy with recombinant activated factor VII—a critical appraisal. *Haemophilia* 2006;12:19–27.
- [46] Kessler C. Haemostasis.com: Clinical experiences in the investigational use of rFVIIa in the management of severe haemorrhage. *Br J Haematol* 2004;127:230.
- [47] Brummel Ziedins K, Rivard GE, Pouliot RL, Butanas S, Gissel M, Parhami-Seren B, Mann KG. Factor VIIa replacement therapy in factor VII deficiency. *J Thromb Haemost* 2004; 2:1735–1744.
- [48] Mariani G, Mazzucconi MG. Factor VII congenital deficiency. Clinical picture and classification of the variants. *Haemostasis* 1983;13:169–177.
- [49] 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(6):899–909.
- [50] Roberts HR. Recombinant factor VIIa (NovoSeven®) and the safety of treatment. *Semin Haematol* 2001;38:48–50.