

## Recombinant factor VIIa for long-term replacement therapy in patients with congenital factor VII deficiency

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Dear Sir,

Some patients with factor VII (FVII) deficiency need long-term prophylaxis. Fresh frozen plasma (FFP) may cause fluid overload and is considered unsuitable. Prothrombin complex concentrates (PCC) show a high variability of FVII levels, and contain other coagulation factors which might increase the thromboembolic risk (1). Plasma-derived FVII concentrates carry the risk of transmission of blood-borne viruses. Prophylactic use of recombinant activated FVII (rFVIIa) to prevent bleedings may therefore be an alternative to minimize the potential risk of transmitting blood-borne viruses. Considering the half-life of plasma-derived FVII (pd FVII) (5-6 hours [h]) and rFVIIa (2-3 h) (2, 3), the frequency of injections necessary to prevent bleeds is another question of interest.

Two patients with congenital FVII deficiency on long-term treatment with rFVIIa (NovoSeven<sup>®</sup>, Novo Nordisk AS, Denmark) were identified in two centres. Patient data were collected by reviewing the records and by additional explorations in July and August 2006 to complete histories. Factor VII coagulant activity (FVII:C) was measured using human coagulation factor VII-deficient plasma supplied by Dade Behring, Marburg, Germany. Blood was collected to rule out inhibitors against rFVIIa or FVII:C. Samples were sent to F. H. Herrmann, Institute for Human Genetics (Ernst-Moritz-Arndt-University Greifswald, Germany), inhibitor assays were performed by J. Ingerslev, University Hospital Skejby/Aarhus, Denmark, as described previously (4). In addition, plasma mixing assays were done at the treatment centres. Genetic analyses were performed by F. H. Herrmann, Ernst-Moritz-Arndt-University Greifswald, Germany.

The two patients with congenital FVII deficiency and FVII:C below 4% received prophylactic treatment with rFVIIa to prevent bleedings (Table 1). No other coagulation disorders were detected. Inhibitors were excluded by negative plasma mixing assay at baseline. After initiation of prophylactic treatment with rFVIIa, no inhibitor was detected. Patients were allowed to perform home treatment. Before starting rFVIIa, bleedings were severe based on the classification suggested by Mariani et al. (5).

*Patient 1*, born in 1987, experienced severe mucosal bleeding, soft tissue haematoma and easy bruising in the first weeks of her life. Initially, she received FFP and red blood cells. Regular prophylaxis with PCC twice weekly (b.i.w.) was started due to a third episode of severe colorectal bleeding. In 1988, prophylaxis was changed to pd FVII three times per week (t.i.w.). Although bleeding tendency decreased, joint bleedings occurred occasionally. Later, menorrhagia had to be treated by pd FVII once or twice daily. For safety reasons, prophylaxis was continued with a recombinant factor VIIa preparation (20 µg/kg rFVIIa t.i.w. and once daily during menses) at the age of 12 years. After six years, the dose was increased to 40 µg/kg rFVIIa due to pressure-induced subcutaneous haematoma. Subsequently, no further bleedings were observed. The peak activity for FVII was higher with 40 µg/kg rFVIIa than with 20 µg/kg rFVIIa and 20 U/kg pd FVII (Fig. 1).

*Patient 2*, born in 1998, experienced mucosal bleedings of the oral cavity and joint bleedings. Therapy was started with pd FVII on demand. At the age of seven years, safety aspects and recurrent joint bleedings (24 per year) as well as epistaxis led to the decision to start prophylaxis with 20 µg/kg rFVIIa b.i.w. or t.i.w. (additional doses for sports). Thereafter, no spontaneous bleedings were observed. Occasionally, slight gingival bleedings during teething occurred. Peak activity reached 208% immediately after administration of 20 µg/kg rFVIIa (Fig. 1).

### Discussion

We report two patients with congenital FVII deficiency and long-term prophylactic treatment with rFVIIa for 14 months and seven years, respectively. Due to the heterogeneity and the rare-

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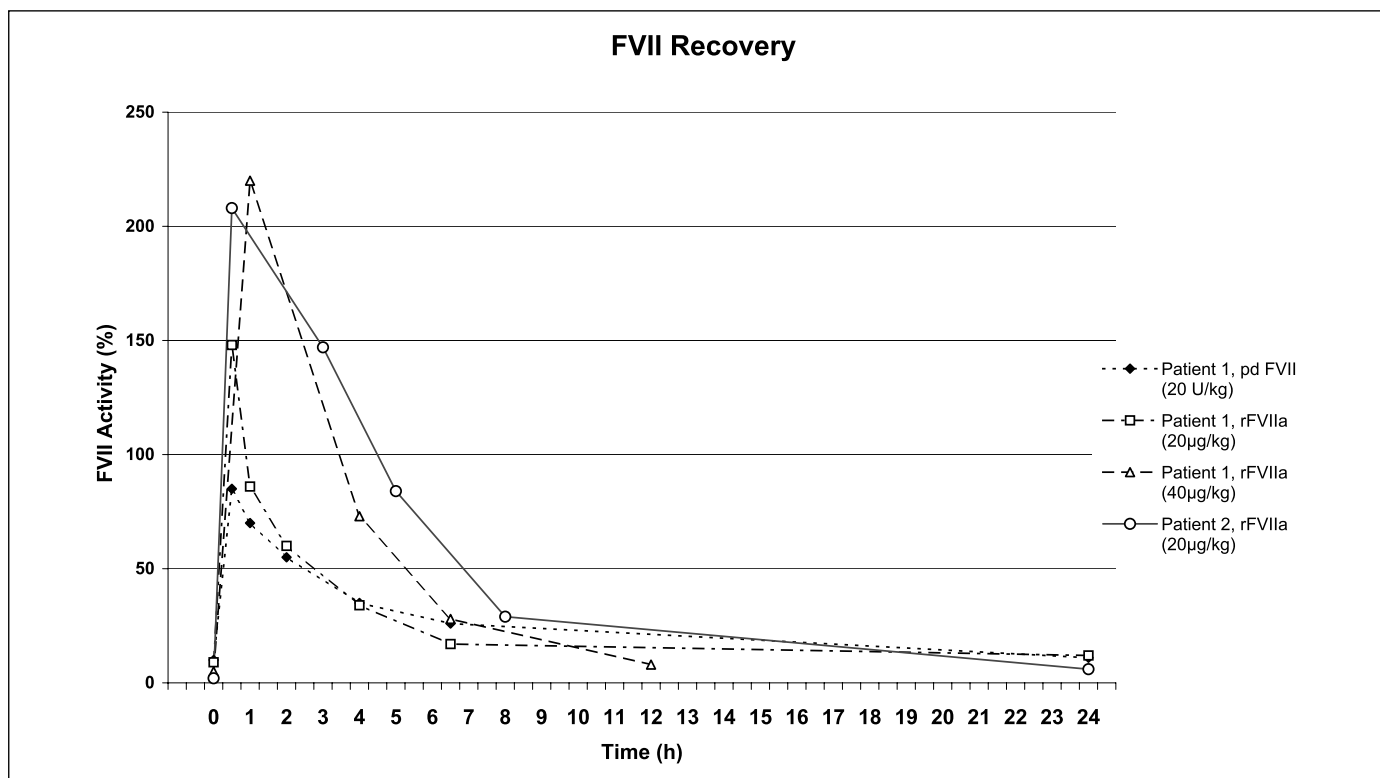
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**Table 1: Patient characteristics and prophylaxis with rFVIIa.**

Parameter	Patient 1	Patient 2
Sex	Female	Female
Age at diagnosis	0 years	0 years
Genetic analyses	Cys135 Arg homozygous	Gly283Ser homozygous
FVII:C	3%	2%
rFVIIa-dose	20 – 40 µg/kg*	20 µg/kg*
Frequency of rFVIIa	t.i.w., and once daily during menses	b.i.w. or t.i.w., and during sports
Duration of rFVIIa	7 years	14 months
Age at last visit while on prophylaxis with rFVIIa	19 years	8 years
Adverse events	None	None

\* dose adapted to size of rFVIIa-vials.



**Figure 1: Recovery of FVII:C in patient 1 (20 U/kg pd FVII, 20 µg/kg and 40 µg/kg rFVIIa) and in patient 2 (20 µg/kg rFVIIa).**

ness of the disease, there is a lack of commonly recognised parameters to determine the bleeding risk even in the surgical setting (6). Therefore, decisions on treatment strategies were mainly based on clinical history and bleeding signs. Even though rFVIIa has a short half-life of about 2–3 h in FVII-deficient patients, and the clearance of rFVIIa seems to be twice as high as in patients with haemophilia A or B (3), injections every 2–3 days were sufficient for long-term prophylaxis in our patients as well as in eight patients published previously (Table 2). Another five published patients with congenital FVII deficiency received once or twice daily prophylaxis, or weekly administrations of rFVIIa (Table 2). An effect of rFVIIa mainly in terms of reduction of bleeding frequency or cessation of bleeding was reported in all 15 patients. Some patients received an intensified regimen with up to twice daily injections of rFVIIa in defined situations including menses or sports. These reports indicate that long-term prophylaxis with about 20 µg/kg rFVIIa given every two to three days offers a superior efficacy in patients with congenital FVII deficiency as compared to prophylaxis with FFP, prothrombin complex concentrates or plasma-derived FVII concentrates.

Special attention should be paid to thromboembolic events. Mariani et al. report a cohort of 514 FVII-deficient patients in which nine thromboembolic events were documented. Six out of these nine events occurred in close coincidence with replacement therapy and surgery: Three patients received PCC, two pd FVII, one FFP and none rFVIIa (7). In seven FVII-deficient patients treated with rFVIIa during 12 consecutive surgical procedures, thrombophlebitis at the site of continuous infusion was

the only complication reported (8). Three spontaneous reports on thromboembolism were received by Novo Nordisk prior to the approval of rFVIIa for the treatment of FVII deficiency (9). At least two out of these patients were treated with higher doses of rFVIIa than recommended (up to 90 µg/kg in one patient and two doses of 50 µg/kg in another patient), which supports the concept of lower rFVIIa-doses in patients with FVII deficiency as compared to patients with haemophilia A or B and inhibitors.

There is a clear advantage of rFVIIa over human plasma-derived products with regard to the transmission of blood-borne viruses. Even though the risks of viral infections (e.g. hepatitis or HIV) have decreased substantially with current plasma-derived products, a relevant concern remains for the patients due to the fact that non-enveloped viruses and parvovirus B 19 are not completely inactivated or removed by currently used manufacturing processes. The observation of a possible association of parvovirus B 19 and arthropathy was supported by observations in patients with haemophilia A reported by Soucie et al. (10).

In summary, rFVIIa should be taken into account if long-term prophylaxis is indicated because of recurrent severe bleeding episodes in FVII-deficient patients. About 15–20 µg/kg rFVIIa (1.2 mg vial in patients weighing 60–80 kg) every two to three days seem to be adequate in most cases. Due to the small number of patients with FVII deficiency who require prophylaxis, experiences should be published or documented in a prospective centralized registry as established by the International Factor VII Study Group (IF7SG) (<http://www.targetseven.org>) or the German FVII Greifswald Registry.

**Table 2: Published efficacy and safety of long-term prophylaxis with rFVIIa.**

Publication*	Patient age <sup>†</sup> /sex	FVII:C	Preceding therapy	rFVIIa			Bleedings after start of rFVIIa	Adverse events
				Dose	Frequency	Duration		
Mathijssen et al. 2004	28 years / f	<1%	PPSB, pd FVII	18 µg/kg	every other day (+ tranexamic acid)	5 years	Decreased	No complications of rFVIIa
	17 years / f	<1%	PCC, pd FVII	19 µg/kg	b.i.w.	2 years	Modest decrease	
Tcheng et al. 2004	15 years / m	<1%	FFP, PCC	80 µg/kg	b.i.w.	5 months	Decreased	Not reported
Michaels et al. 2005	9 years / f	1.5%	pd FVII, PCC	20 – 40 µg/kg	every 3 days	4 years	1 muscle bleed in 4 years	Transient arm pain after first infusion
Holve et al. 2001 Congress abstract	>10 years / f	<1%	FFP, pd FVII	22 µg/kg	every 3 days, menses: once daily	1 year	Controlled	Not reported
	>7 years / m	<1%	FFP, pd FVII	20 µg/kg	every 3 days	1 year	Excellent control	
Karayalcin and Hart 2002 Congress abstract	4 years / m	<1%	FFP, APCC, PCC	25 µg/kg	t.i.w.	3 years	No major bleedings	No thrombotic events
Recht et al. 2002 Congress abstract	1 year / m	<1%	rFVIIa, only	30 µg/kg	every 3 days	9 months	None	Not reported
Berry et al. 2001 Congress abstract	1 year / f	< 0.1 U/ml	None	15 – 50 µg/kg	twice daily	>16 months	None	No thrombotic events
Halsey et al. 2002 Congress abstract	1 year / m	<1%	rFVIIa, only	60 µg/kg	once daily	15 months	None	Not reported
Dhawan et al. 2004	10 months / m	< 1 U/dL	None	59 µg/kg	twice daily <sup>#</sup>	Approx. 10 months	None reported	After hepatocyte transplantation: sepsis, catheter infections together with thromboses
	3 years / m	< 1 U/dL	None	29 µg/kg	twice daily <sup>#</sup>	Approx. 3 years		
Salcioglu-Zafer et al. 2005 Congress abstract	3 years / m	Not given	FFP	Not given	once weekly	8 months and 7 months	Four minor mucosal bleedings in 8 months and no bleedings in 7 months	Not reported

\* List of references available at the authors. <sup>†</sup>Age at last visit while on prophylaxis with rFVIIa. <sup>#</sup>After hepatocyte transplantation dose requirements were reduced to 28 – 35 µg/kg/day rFVIIa (1<sup>st</sup> patient) and 13 – 17 µg/kg/day rFVIIa (2<sup>nd</sup> patient).

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## Erratum

In the Letter to the Editor by Rossi et al. published in the September issue of *Thrombosis and Haemostasis* (*Thromb Haemost* 2007; 98: 695-697) an error occurred during correction of the

proofs. On page 1, column 1, line 31 it should be "...since the AT progressive assay is NOT recommended..." instead of "...since the AT progressive assay is recommended...".