Replacement therapy for bleeding episodes in factor VII deficiency

A prospective evaluation

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Summary

Patients with inherited factor VII (FVII) deficiency display different clinical phenotypes requiring *ad hoc* management. This study evaluated treatments for spontaneous and traumatic bleeding using data from the Seven Treatment Evaluation Registry (STER). One-hundred one bleeds were analysed in 75 patients (41 females; FVII coagulant activity <1–20%). Bleeds were grouped as haemarthroses (n=30), muscle/subcutaneous haematomas (n=16), epistaxis (n=12), gum bleeding (n=13), menorrhagia (n=16), central nervous system (CNS; n=9), gastrointestinal (GI; n=2) and other (n=3). Of 93 evaluable episodes, 76 were treated with recombinant, activated FVII (rFVIIa), eight with fresh frozen plasma (FFP), seven with plasma-derived FVII (pdFVII) and two with prothrombin-complex concentrates. One-day replacement therapy resulted in very favourable outcomes in haemarthroses, and was successful in muscle/subcutaneous haematomas, epistaxis and gum bleeding. For menorrhagia, single- or multiple-dose schedules led to favourable outcomes. No thrombosis occurred; two inhibitors were detected in two repeatedly treated patients (one post-rFVIIa, one post-pdFVII). In FVII deficiency, most bleeds were successfully treated with single 'intermediate' doses (median 60 µg/kg) of rFVIIa. For the most severe bleeds (CNS, GI) short- or long-term prophylaxis may be optimal.

Keywords

Bleeds, replacement therapy, factor VII deficiency

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Introduction

Inherited factor VII (FVII) deficiency is the most common of the rare autosomal recessive bleeding disorders, with an estimated prevalence of one per 300,000–500,000 in European countries; clinical features have been clearly defined in a number of recent publications (1-4). It is likely that the prevalence is higher in those countries where consanguineous marriages are frequent, especially with respect to the severe forms of the disease (5).

Affected patients display a wide range of clinical phenotypes, from an asymptomatic condition to serious haemorrhagic episodes, such as fatal central nervous system (CNS), gastrointestinal (GI) or "spontaneous" joint and muscle bleeds (6, 7). Symptomatic patients can be divided into two major categories: those with a mild to moderate bleeding tendency and individuals with a very clear bleeding tendency that may be more severe than in haemophilia. The former group will experience mainly mucosal bleeding, a clinical picture that mimics that of a platelet disorder and often does not necessitate treatment. In contrast, for the most severely affected patients suffering from life- or limb-threatening haemorrhages, aggressive replacement therapy (RT) and/or long-term prophylaxis is required. Patients with clinically severe FVII deficiency commonly become symptomatic at a young age (e.g. soon after birth or in the first two years) and have low to very low levels of residual FVII, which are associated with severe causative F7 gene lesions (2, 7).

In congenital bleeding disorders (CBD), the mainstay for bleeding management is RT based on the substitution of the missing factor, with the aim of correcting the clotting defect. For the management of FVII deficiency, a number of RTs (3), from plasma or plasma-derived to recombinant products, can be used. However, limited information is available regarding optimal treatment schedules and dosing as well as indications, treatment limitations and adverse events (8, 9). We have therefore prospectively collected data from the Seven Treatment Evaluation Registry (STER) on large numbers of treatments for spontaneous or traumatic bleeding episodes and evaluated therapy schedules and adverse events.

Materials and methods

The STER is a prospective, observational, multicentre, Web-based registry created to collect and describe data on treatment modalities and outcomes in patients with congenital FVII deficiency. As treatment decisions, especially in rare CBD, are mostly based on personal clinical experience rather than on consolidated clinical evidence, the general purpose of the STER is to document treatment practices for "spontaneous" bleeds, surgery, prophylaxis and related adverse events. Since only a limited number of patients are available for follow-up in most treatment centres, the STER aims to elucidate treatment modalities in a well-defined population of FVII-deficient patients, carefully characterised according to their clinical and clotting phenotypes. The study protocol was created following strictly controlled data collection procedures set up by the International FVII Deficiency Study Group (IF7SG) based on the experience gained from previous studies (6, 7, 10, 11). Data collected online are stored in a custom designed database. The STER system is a Web application and data are stored in a Microsoft SQL Server 2000 database, which contains the electronic case report form pages with no components installed on the centre computers. Investigators access the system when a patient needs a treatment for: (i) spontaneous bleeding episodes; (ii) prophylaxis courses; and (iii) surgical interventions. For spontaneous (or traumatic) bleeding episodes, the study protocol was designed to capture the following items: (i) type of bleeding; (ii) treatment site (home vs. hospital); (iii) relation to trauma; (iv) detail regarding substitution therapy; (v) concomitant medications (i.e. anti-fibrinolytics); (vi) concomitant illness; and (vii) adverse events (e.g. anaphylactoid reactions, inhibitor occurrence, thrombotic events, disseminated intravascular coagulation, bleeding and mortality).

In order to evaluate only those subjects with a clear risk of bleeding (10, 11), only patients with FVII coagulant activity (FVIIc) levels ≤20% were considered (▶Table 1). Enrolment occurred only if the treating physician considered RT necessary to treat a bleeding episode. FVIIc was assayed at each participating centre using high-sensitivity thromboplastins in every instance (ISI~1). Patients were also carefully characterised with respect to their bleeding phenotype by recording the number and type of different symptoms reported (▶Table 1). The following RT parameters were evaluated: (i) RT duration (days); (ii) total number of RT injections; (iii) total RT dose; (iv) mean daily dose (total dose/number of treatment days); and (v) mean single dose (total dose/number of injections) (▶Table 2 and ▶Table 3). Treating physicians performed bleeding diagnosis and management. Thrombosis diagnosis (venous or arterial) was based on clinical suspicion and confirmed by imaging. Screening for inhibitory antibodies to FVII was carried out in a central laboratory using a standard assay (Aarhus University Hospital, Skejby, Denmark and, after January 2010, Guy's & St. Thomas' Hospital, London, UK) of baseline and 30-day plasma samples. The method used is a modification of the Bethesda assay, sensitive to 0.45 Bethesda units (BU) of inhibitor, where 1 BU is the antibody amount capable of reducing FVII by 50% after 2 hours (h) of incubation (12). The reference used to detect inhibitors to FVII was a pool of "normal" plasma. The inhibitor assay was not performed if baseline FVIIc levels were >4%.

New records were reviewed by an adjudication committee (GM, AD) and an expert from the Central Records Office (see Acknowledgements), and investigators were asked to complete the file blanks prior to definitive approval. In order to provide information useful to the treating physicians, bleeding episodes were grouped into the following categories: (i) haemarthroses; (ii) muscle and subcutaneous haematomas; (iii) menorrhagia; (iv) epistaxis; (v) gum bleeding; (vi) CNS and GI; (vii) other.

Efficacy evaluation was performed 6 h after RT, according to the following criteria:

- Excellent: Single administration leading to cessation of overt bleeding and of related symptoms; prompt (within a few hours) relief of pain; disappearance of swelling and return to the previous range of joint or limb mobility. Cessation of bleeding was also evaluated by imaging if appropriate.
- Effective: More than one administration was needed to obtain the same results as above.
- Partially effective: More than one administration was needed, but symptoms subsided slowly and the return of limb and joint mobility was partial.
- Ineffective: There were no changes.
- Not evaluable: No elements for evaluation were available.

The number of doses was considered the most important element in the outcome evaluation. For menorrhagia, treatment evaluation was performed after the end of the cycle. The research proposed by the STER Study Group was approved by the Ethics Committee of L'Aquila University (coordinator's previous institution) and, in parallel, by the committees of the other institutions involved. The STER protocol is publicly available at http://www.targetseven.org and published on http://clinicaltrials.gov (# NCT01269138).

Statistical analysis

Statistical descriptive measures, including the mean or median and range (variability), were calculated for each parameter evaluated, and performed using the MedCalc® software version 7.4.1.2 (Mariakerke, Belgium; http://www.medcalc.be).

Table 1: Demographics and clinical and clotting phenotypes.

Patient number	Gender	Age (years)	FVIIc (%)	Number of recorded symptoms	Type of recorded symptoms
1	Female	12	<1.0	4	Br; Hr; Hp; Me
2	Male	3	<1.0	5	Br; Ep; Gu; Mu; Sc
3	Female	6	<1.0	2	CNS; Gu
4	Female	46	<1.0	3	Ep; Gu; Me
5	Female	1	<1.0	2	CNS; Um
6	Male	64	<1.0	5	Gi; Gu; Hr; Hm; Mu
7	Female	22	<1.0	1	Me
8	Male	13	<1.0	7	Br; Ep; Gi; Gu; Hr; Mu; Sc
9	Female	20	<1.0	5	Br; Ep; Gu; Hm; Me
10	Female	19	<1.0	5	Br; Ep; Gu; Hm; Me
11	Female	23	<1.0	1	Me
12	Male	59	<1.0	4	Br; Ep; Gi; Hr
13	Female	7	<1.0	2	Hr; Mu
14	Female	20	<1.0	2	Gi; Me
15	Male	29	<1.0	1	Gi
16	Female	5	<1.0	6	CNS; Br; Ep; Gi; Gu; Mu
17	Female	54	<1.0	6	Br; Ep; Gum; Hp; Hb; Me
18	Female	8	<1.0	2	Hr; Sc
19	Female	4 days	<1.0	4	Br; Gi; Sc; Um
20	Female	11	1.0	6	Ep; Gu; Hr; Me; Mu; Sc
21	Male	7	1.0	1	Hr
22	Female	5	1.0	1	Hr
23	Female	45	1.0	3	CNS; Br; Me
24	Female	58	1.0	9	CNS; Br; Gu; Hr; Hm; Hb; Me; Mu; Sc
25	Male	0.1	1.0	1	Gi
26	Female	71	1.0	4	Br; Ep; Gu; Mu
27	Female	48	1.0	2	Hr; Mu
28	Female	17	1.0	3	Ep; Gu; Me
29	Female	13	1.0	2	Ep; Gu
30	Male	16	1.0	2	Ep; Gu
31	Male	7	1.0	1	Ep
32	Female	0.2	1.0	2	CNS; Gi; Hb
33	Male	0.6	1.1	1	CNS
34	Female	21	1.3	6	Ep; Gum; Hr; Me; Mu; Sc
35	Male	0.4	1.3	1	Gi; Gu
36	Female	5	1.4	1	Br
37	Female	0.5	1.5	3	CNS; Gu; Sc
38	Female	14	1.6	1	Gu
39	Female	7	1.7	9	Br; Ep; Gi; Gu; Hr; Hm; Mu; Sc; Um
40	Male	7	1.7	7	Br; Ep; Gi; Hr; Hm; Mu; Sc
41	Female	7	2.0	2	Br; Gu
42	Male	1.1	2.0	3	Br; Mu; Sc

Table 1: continued

Patient number	Gender	Age (years)	FVIIc (%)	Number of recorded symptoms	Type of recorded symptoms
43	Female	7	2.0	3	Br; Ep; Mu
44	Male	12	2.0	2	Ep; Gu
45	Male	18	2.0	2	Ep; Gu
46	Female	1.5	2.1	2	Ep; Mu
47	Male	12.5	2.2	5	Br; Ep; Gi; Gu; Hr
48	Male	6	2.4	7	Br; Ep; Gu; Hr; Mu; Sc; Um
49	Male	11	2.5	5	Ep; Gi; Gu; Hr; Mu
50	Female	13	2.5	3	Br; Ep; Gu
51	Female	13	2.5	1	Hr
52	Male	1	2.5	6	CNS; Br; Ep; Gu; Mu; Sc
53	Female	13	2.7	7	CNS; Br; Ep; Gu; Hr; Me; Sc
54	Female	19	3.0	5	Br; Ep; Gu; Me; Mu
55	Female	4	3.0	2	Mu; Sc
56	Male	32	3.0	2	CNS; Hr
57	Male	32	3.0	2	CNS; Hr
58	Male	32	3.0	2	CNS; Hr
59	Male	32	3.0	2	CNS; Hr
60	Male	2	3.0	1	Br
61	Male	10	3.0	1	Hr
62	Male	8	3.0	1	Hr
63	Female	11	3.0	6	Br; Ep; Gu; Hr; Mu; Sc
64	Male	32	3.0	2	CNS; Hr
65	Female	11	4.0	1	Hp
66	Female	44	4.0	1	Me
67	Female	25	5.0	6	Br; Ep; He; Me; Sc; Um
68	Male	4	5.0	7	CNS; Br; Gi; Gu; Mu; Sc; Um
69	Male	40	5.7	2	Ep; Hr
70	Female	59	7.0	1	Mu
71	Male	17	9.0	1	Gu
72	Male	3	9.0	1	Ep
73	Male	2	17.0	1	Ep
74	Male	4	20.0	1	Ep
75	Male	46	20.0	1	Hb

Br, bruising; CNS, central nervous system bleeding; Ep, epistaxis; FVIIc, FVII coagulant activity; Gi, gastrointestinal bleeding; Gu; gum; Hb, haemorrhoidal bleeding; He, haematuria; Hm, haemorrhoidal; Hp,haemoperitoneum; Hr,haemarthrosis; Me, menorrhagia; Mu, muscle; Sc, subcutaneous haematoma; Um, umbilical bleeding.

Results

As of January 2012, management for 101 bleeds performed in 23 haemophilia treatment centres from 15 countries was observed in 75 patients with FVII deficiency (41 females and 34 males, age range 0·1–71 years), with residual FVIIc levels ranging between <1 and 20% (▶Tables 1, 2 and 3). All patients were previously symptomatic, with a wide array of symptom combinations (▶Table 1). Fifty-two patients (51%) were treated once, 19 patients twice, seven patients three and four times and, finally, 16 patients were treated five times or more. Detailed clinical and clotting phenotypes are shown in ▶Table 1 (patients' reference numbers given in

Table 2: rFVIIa schedules and outcome by bleeding type.

Symptom and patient number (ref. Table 1)	Trauma	Replacement therapy schedule				Anti-fibrinolytics	Outcome	Adverse event
		Days (n)	Total number of doses	Total dose (µg/kg)	Mean dose (µg/kg)			
CNS bleeding								
23	No	1	8	160	20	No	Partly effective	No
3	Yes	1	3	90	30	No	Effective	No
32	No	14	87	2,610	30	No	Effective	No
32	No	3	6	90	15	No	Effective	No
19	No	2	8	240	30	No	Excellent	No
35	No	1	3	90	30	No	Effective	No
15	No	1	8	160	20	No	Effective	No
47	No	1	8	200	25	No	Effective	No
Haemarthrosis								
8	No	1	2	120	60	No	Effective	No
18	Yes	1	3	240	80	No	Effective	No
21	No	1	5	300	60	No	Effective	No
22	No	1	7	210	30	No	Effective	No
24	No	1	1	18	18	No	Excellent	No
39	Yes	1	1	28	28	No	Excellent	No
26	Yes	1	1	30	30	No	Excellent	No
26	Yes	1	5	90	18	No	Effective	No
56	No	2	2	120	60	No	Effective	No
56	No	1	1	60	60	No	Excellent	No
56	No	1	1	60	60	No	Excellent	No
48	Yes	2	2	104	52	No	Effective	No
69	No	1	1	30	30	No	Partly effective	No
57	No	1	1	60	60	No	Excellent	No
57	No	1	1	60	60	No	Excellent	No
57	No	1	1	60	60	No	Excellent	No
34	Yes	1	1	20	20	No	Excellent	No
58	No	2	4	180	45	No	Effective	No
58	No	1	1	60	60	No	Excellent	No
58	No	1	1	60	60	No	Excellent	No
59	No	1	1	60	60	No	Excellent	No
59	No	1	2	120	60	No	Effective	No
59	No	1	1	60	60	No	Excellent	No
63	No	1	1	35	35	No	Excellent	Re-bleeding
64	No	3	3	180	60	No	Partly effective	No
42	No	1	4	100	25	No	Effective	No
6	No	1	1	10	10	No	Excellent	No

Table 2: continued

Symptom and patient number (ref. Table 1)	Trauma	Replacement therapy schedule				Anti-fibrinolytics	Outcome	Adverse event
		Days (n)	Total number of doses	Total dose (μg/kg)	Mean dose (μg/kg)			
Haematomas (muscle and subcutaneous)								
27	No	1	1	26	26	No	Excellent	No
70	No	1	2	26	13	No	Effective	No
48	Yes	1	1	54	54	No	Excellent	No
40	Yes	1	1	57	57	No	Excellent	No
52	Yes	1	1	65	65	No	Excellent	Inhibitor
2	Yes	1	1	80	80	No	Excellent	No
13	Yes	1	3	75	25	No	Effective	No
37	No	1	3	60	20	No	Effective	No
42	Yes	1	4	100	25	No	Effective	No
Menorrhagia								
20	No	3	4	50	12.5	Yes	Excellent	No
20	No	2	4	50	12.5	Yes	Excellent	No
7	No	1	1	20	20	No	Effective	No
7	No	1	1	20	20	No	Effective	No
7	No	1	1	270	270	No	Effective	No
11	No	1	1	20	20	No	Excellent	No
1	No	6	8	80	10	Yes	Excellent	No
1	No	3	5	40	8	Yes	Effective	No
14	No	2	8	240	30	No	Effective	No
28	No	1	2	60	30	No	Effective	No
4	No	1	2	90	45	No	Effective	No
34	No	1	1	41	41	No	Excellent	No
34	No	1	1	20	20	No	Excellent	No
66	No	1	8	240	30	No	Effective	No
Gum bleeding								
48	No	1	1	52	52	No	Excellent	No
38	No	1	1	30	30	No	Excellent	No
71	No	1	2	60	30	No	Effective	No
44	No	1	1	30	30	No	Excellent	No
29	Yes	1	1	30	30	No	Excellent	No
30	No	1	2	60	30	No	Effective	No
45	No	1	1	50	50	No	Excellent	No
45	No	1	1	50	50	No	Excellent	No

►Table 1 are reported in ►Tables 2 and 3). There was a higher percentage of females than males (54.7% vs. 45.3%), (►Table 1). Eighty-eight percent of patients had FVIIc levels below 5%. Of the 101 bleeds, 93 were fully evaluable and eight (three treated with recombinant activated factor VII [rFVIIa; NovoSeven®, Novo Nordisk A/S, Bagsvaerd, Denmark], four with fresh frozen plasma [FFP; provided locally by the blood transfusion services] and one with prothrombin complex concentrate [PCC; Prothromplex™, Baxter, Deerfield, IL, USA]) were evaluated for adverse events only. Of the 30 haemarthroses, seven were reported as 'traumatic',

Table 2: continued

Symptom and patient number (ref. Table 1)	Trauma	Replacement therapy schedule				Anti-fibrinolytics	Outcome	Adverse event
		Days (n)	Total number of doses	Total dose (μg/kg)	Mean dose (μg/kg)			
Epistaxis								
42	No	1	2	50	25	No	Effective	No
31	No	1	1	60	60	No	Excellent	Re-bleeding
31	No	1	8	480	60	No	Effective	No
16	No	1	2	40	20	No	Effective	No
74	No	1	2	180	90	Yes	Effective	Re-bleeding
73	No	1	1	90	90	Yes	Excellent	No
53	No	1	1	26.6	26.6	No	Excellent	No
43	No	1	1	66	66	No	Excellent	No
72	No	1	1	160	160	No	Excellent	No
72	No	1	1	142	142	No	*Not evaluable*	No
45	No	1	1	50	50	No	*Not evaluable*	No
Others								
Haemorr. bleed 75	No	12	75	3,600	48	Yes	*Not evaluable*	No
Easy bruising 60	Yes	1	4	120	30	No	Effective	No

CNS, central nervous system; Haemorr, haemorrhoidal; rFVIIa, recombinant activated factor VII.

as were 10 of the 16 muscle and subcutaneous haematomas, two of the 13 gum bleeds and one patient with easy bruising (►Table 2 and ►Table 3).

Recombinant FVIIa was given to treat 79/101 episodes (room temperature stable rFVIIa in five [►Table 2 and ►Table 4]); plasma-derived FVII (pdFVII) concentrates (Provertin™, Baxter or Facteur VII, LFB, Lille, France) were used in seven, FFP in 12, and PCC in three bleeding episodes (►Table 3 and ►Table 4). Outcomes with rFVIIa were excellent in 38 and effective in 35 of the 79 cases (partly effective in three and not evaluable in three others). Plasma-derived FVII concentrates were associated with excellent outcomes in three, effective in three and partially effective in one of the seven cases. Of the eight evaluable cases treated with FFP, outcome was effective in seven cases and partially effective in one. PCC provided an excellent outcome in two cases (the third was not evaluable). RT data and outcomes are summarised in ►Table 4. Four cases of re-bleeding were reported, three of which were treated with rFVIIa (►Table 2), and one with FFP (►Table 3): in one case re-bleeding was traumatic (heel) as it occurred at another site, but did not require further treatment; in two cases re-bleeding occurred after one-day RT for epistaxis; the fourth case was treated with one-day FFP treatment for gum bleeding that relapsed after 24 h. One patient received a prolonged RT for a haemorrhoidal bleeding, a problem that was surgically resolved.

Concomitant administration of anti-fibrinolytic agents was reported in 10 patients (six with menorrhagia, three with epistaxis and one with haemorrhoidal bleeding). Only one patient with menorrhagia was on the combined contraceptive pill.

No thrombotic episodes were reported during the 30-day follow-up. Two inhibitors were detected 30 days after RT (maximum titres: 2.1 and 22.4 BU).

Discussion

Randomly occurring bleeding episodes, either 'spontaneous' or traumatic, represent the current treatment requirement for patients with a CBD. These 'non-surgical' bleeds may be sporadic or recurrent, depending on the severity of the disease and environmental events (13). In patients with haemophilia, the vast majority of all bleeding episodes occur in the joints and muscles (13, 14), but in autosomally transmitted bleeding disorders, the clinical picture is more varied, comprising mild, muco-cutaneous bleeds, but also other limb- or life-threatening bleeds (1-4, 6, 7). All patients described in this study were previously symptomatic and some of them exhibited almost the entire array of bleeds described in FVII deficiency (7). These composite clinical pictures were confirmed by clotting phenotypes characterized by FVIIc levels <5% in 88% of the patients. Our study cohort is representative of the spectrum of symptoms observed in FVII deficiency, especially in its more severe manifestations.

Haemarthroses in FVII deficiency display the same clinical features as in haemophilia, but the overall frequency (≈10%) of this

Table 3: Plasma and plasma-derived concentrates use and outcome by bleeding type.

Drug and patient number (ref. Table 1)	Symptoms	Trauma	Replacement therapy schedule				Anti-fibrinolytics	Outcome	Adverse event
			RT days (n)	Total number of doses	Total dose	Mean dose			
FFP §									
33	CNS bleeding	No	1	1	15	15	No	Effective	No
68	GI bleeding	No	1	1	33	33	No	*Not evaluable*	No
41	Gum bleeding	No	1	1	10	10	No	Effective	No
50	Gum bleeding	No	1	2	20	10	No	Partly effective	No
50	Gum bleeding	No	1	2	35	17.5	No	*Not evaluable*	Re-bleeding
51	Haemarthrosis	No	1	2	20	10	No	*Not evaluable*	No
61	Haemarthrosis	No	1	1	10	10	No	Effective	No
54	Haematomas *	No	1	2	20	10	No	Effective	No
46	Haematomas *	No	6	12	120	10	No	*Not evaluable*	No
55	Haematomas *	No	1	2	20	10	No	Effective	No
41	Menorrhagia	No	1	1	10	10	Yes	Effective	No
62	Haematoma *	Yes	1	1	10	10	No	Effective	No
PCC °									
49	Haemarthrosis	Yes	1	1	38	38	No	Excellent	No
39	Haematomas *	Yes	1	1	30	30	No	Excellent	No
26	Haematomas *	Yes	1	1	30	30	No	*Not evaluable*	No
pdFVII^									
74	Epistaxis	No	1	2	56	28	Yes	Effective	No
12	GI bleeding	No	2	3	60	20	No	Effective	No
17	Gum bleeding	Yes	1	1	33	33	No	Excellent	Inhibitor
10	Gum bleeding	No	1	1	21	21	No	Excellent	No
74	Haematomas *	Yes	1	2	56	28	No	Effective	No
67	Haematuria	No	1	1	18	18	No	Excellent	No
9	Menorrhagia	No	3	4	133	33	Yes	Partly effective	No

CNS, central nervous system; FFP, fresh frozen plasma; GI, gastrointestinal; musc, muscle; PCC, prothrombin complex concentrate; pdFVII, plasma-derived FVII; RT, replacement therapy; subcut, subcutaneous. * Muscle and Subcutaneous; § ml/Kg; ° IU; ^ IU

crippling haemorrhage appears reduced in comparison to that observed in severe haemophilia (7). However, if only patients with residual FVIIc levels <2% are considered, the difference is reduced (14/40 [35%] in this study and 42/117 [35.9%] in the IRF7 cohort). A distinctive feature in FVII deficiency is that haemarthroses occur, for obvious genetic reasons, with comparable prevalence in males (20.7%) and females (18.6%) (7). Furthermore, those patients with recurrent joint bleeds were shown to have very low FVIIc levels (7), a feature that is confirmed in this analysis (►Table 1). Regarding treatment, the schedules adopted were mostly based on a single-day/single-dose treatment (15/27, 55%). On average, the dose of rFVIIa associated with excellent outcomes was intermediate (median 60 μg/kg), higher than expected, but one should consider that haemostasis was ensured with one bolus of a factor with a very short half-life. Ten equally effective treatments were performed with schedules based on multiple and higher dosages (median 120 μg/kg) (►Table 4). Therefore, the overall favourable response rate of joint bleeds to rFVIIa treatment can be considered very satisfactory (92%).

Haematomas (muscle or subcutaneous) can be as painful as haemarthroses and, if large enough, can cause compartment syndrome, muscle fibrosis and contractures. For the nine patients treated with rFVIIa, an efficacious one-day schedule (one to three doses) was used with a total dose equal to that used for joint bleeds (median ≈60 μg/kg) (►Table 4); treatments with PCC (n=3) or FFP (n=12) appeared less effective but, given the small number of patients, firm conclusions cannot be drawn (►Table 3 and ►Table 4).

Table 4: Summary of treatments.

Treatment	N	Days of treatment (median and range)	Number of doses (median and range)	Total dose		Outcome				
				Median	Range	Excellent (1 dose)	Effective (>1 dose)	Partially effective	Ineffective	Not evaluable
rFVIIa	79	1 (1–14)	1 (1–87)	60 µg/kg	10–3600	38	35	3	–	3
Haemarthrosis	27	1 (1–3)	1 (1–7)	60 µg/kg	10–300	15	10	2	–	–
Menorrhagia	14	1 (1–6)	2 (1–8)	50 µg/kg	20–270	6	8	–	–	–
Epistaxis and gum bleeding	19	1 (1–1)	1 (1–8)	52 µg/kg	27–480	12	5	–	–	2
CNS	8	1 (1–14)	8 (3–87)	160 µg/kg	90–2610	1	6	1	–	–
Haematomas (muscle and sub-cutaneous)	9	1 (1–1)	1 (1–3)	60 µg/kg	26–100	5	4	–	–	–
Other	2	1 (1–12)	4 (4–75)	120 µg/kg	100–3600	–	2	–	–	1
FFP	12	1 (1–6)	1 (1–12)	15 ml/kg	10–120	–	7	1	–	4
pdFVII	7	1 (1–3)	2 (1–4)	56 IU	21–133	3	3	1	–	–
PCC	3	1 (1–1)	1 (1–1)	30 IU	30–38	2	–	–	–	1

CNS, central nervous system; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; pdFVII, plasma-derived FVII; rFVIIa, recombinant activated factor VII.

Menorrhagia is highly prevalent in patients with CBD (60–100% of cases, depending on disease type and severity). This frequent bleeding symptom seriously impairs patients' quality of life and can cause iron-deficient anaemia in the medium or long term (15). Menorrhagia is also highly prevalent in FVII-deficient patients (63% of the cases in the fertile age) (7), with a clear relationship with FVIIc levels: women with menorrhagia were shown to have significantly lower FVIIc levels than those without (4.5% vs. 14%, $p<0.001$) (7). Furthermore, girls with FVIIc <9% carry a five-fold risk of developing menorrhagia in comparison to those with higher FVIIc levels (7). In the present study, RT with rFVIIa for menorrhagia provided satisfactory results: the outcome was excellent in six and effective in eight of the 14 cases. However, of note is that substitution does not aim to stop bleeding but to reduce it, and since quantitative evaluation of menstrual blood loss is not currently performed, it is not possible to determine the extent to which blood loss was reduced. RT duration varied from one-day (9/14 cases) to multiple-day administrations (two days: 2/14 cases; ≥3 days: three cases), with no apparent difference in efficacy. As with haemarthroses, intermediate, total doses of 50 µg/kg were associated with efficacious outcomes (►Table 4). From these data, it appears that schedules based on single or multiple administrations in the first day of the cycle are not inferior to multiple-day schedules, but this finding needs to be substantiated by larger studies and objective measurements.

Epistaxis and gum bleeding are very frequent symptoms of FVII deficiency (7) that are usually managed with local measures (tampons, anti-fibrinolytics), but may sometimes require RT. Considering the small number of reports on these bleeds available, we have evaluated these two mucosal bleeds together; rFVIIa was employed with excellent or effective outcomes (17/19 patients), and pdFVII appeared equally effective (►Table 3 and ►Table 4). Other treatments for muco-cutaneous bleeds have been reported (►Table 3 and ►Table 4), but numbers are too small to draw conclusions.

Although the treatment of most of the episodes of CNS bleeds (8/9) was reported to be satisfactory (one excellent, six effective and one partially effective), due to the short RT duration, firm conclusions on outcomes cannot be drawn. As reported in previous studies (2, 6, 7, 16), these bleeding episodes occur mostly in unweaned or young babies and require intense RT schedules, i.e. short- or long-term prophylaxis courses; therefore, on-demand treatment does not appear to be the best choice.

Overall, rFVIIa administrations yielded excellent (i.e. one day/one dose) responses in 38/79 (48%) and effective responses in 35 (44%) bleeds, with median dosages of 60 µg/kg (►Table 4). The need for medium to high doses may be explained by the short half-life (mean half-life: 2.73 h [11 individuals]) and the low *in vivo* recovery (mean 0.59 [90 individuals]) for rFVIIa observed in a study in progress (17). Plasma-derived FVII concentrates may provide an alternative to rFVIIa, but little experience has been gained in this study and availability is becoming a problem (►Table 4).

As the number of patients treated with plasma or plasma-derived concentrates was limited, a formal comparison between rFVIIa and the other substitutions was not possible. It is evident that FFP, though used in children, was not associated with satisfactory results, but one has to consider that in some countries this is

What is known about this topic?

- Previously, patients with inherited factor VII (FVII) deficiency were poorly characterised from a clinical standpoint, and only anecdotal evidence was available on schedules and dosages.
- Reported treatments with recombinant FVIIa (rFVIIa) were from retrospective collation of data.
- Very little was known in terms of fresh frozen plasma use.
- Single, anecdotal data only were available on the development of inhibitors to FVII.
- No data were available on thrombosis occurrence.

What does this paper add?

This paper provides

- a clear-cut definition of the clinical picture of FVII deficient patients and of bleeding episodes needing treatment.
- useful indications on schedules and dosages for rFVIIa, focussed on the most frequent bleeds.
- insights into the limitations and efficacy of FFP.
- preliminary data on the prevalence of inhibitor occurrence.
- preliminary, though meaningful, data on the rarity of thrombotic events in these patients.

the only choice available. Concomitant anti-fibrinolytics were used in too few patients to allow an efficacy evaluation.

No thrombotic episodes were reported to be associated with any type or RT dose in any of the patients, even prior to this study. Two inhibitors were detected, one after rFVIIa and the other after pdFVII, in two repeatedly treated patients: including this study, three inhibitors have been detected so far. While the inhibitor prevalence in FVII deficiency appears to be in the range of that reported for haemophilia B, the lack of a definitive denominator in our still on going study does not allow any firm conclusions to be drawn. Of note, no anaphylactoid reactions were reported, notwithstanding the similar structure of the missing factor and the fact that all of the inhibitor patients continued to be treated after the inhibitor detection.

To conclude, most bleeding episodes in patients with FVII deficiency can be successfully treated, with a good safety outcome, using a single-day, single-dose schedule of rFVIIa at 'intermediate' doses. Although side effects are very rare, screening for inhibitors to FVII is recommended.

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Conflicts of interest

BS is currently an employee of Baxter Healthcare. At the time the study was conducted he participated in advisory boards and/or received speaker honoraria from Novo Nordisk, Baxter, CSL Behring, Quintiles, Paion, Bayer, TEM innovations and Swedish Orphan Biovitrum. The Haemostasis Research Unit at which Dr Sørensen used to work received unrestricted research support from Novo Nordisk, Grifols, CSL Behring, LFB, Baxter, Bayer Swedish Orphan Biovitrum and Octapharma. GM, GDM and JI participated in meetings organized by Novo Nordisk and received honoraria. JB is an employee at Novo Nordisk. The other authors do not have conflict of interest to disclose.

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