Women with congenital factor VII deficiency: clinical phenotype and treatment options from two international studies

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Abstract

Introduction: A paucity of data exists on the incidence, diagnosis and treatment of bleeding in women with inherited factor VII (FVII) deficiency.

Aim: Here we report results of a comprehensive analysis from two international registries of patients with inherited FVII deficiency, depicting the clinical picture of this disorder in women and describing any gender-related differences.

Methods: A comprehensive analysis of two fully compatible, international registries of patients with inherited FVII deficiency (International Registry of Factor VII deficiency, IRF7; Seven Treatment Evaluation Registry, STER) was performed.

Results: In our cohort (*N*=449; 215 male, 234 female), the higher prevalence of mucocutaneous bleeds in females strongly predicted ensuing gynaecological bleeding (hazard ratio=12.8, 95% CI 1.68–97.6, *P*=0.014). Menorrhagia was the most prevalent type of bleeding (46.4% of patients), and was the presentation symptom in 12% of cases. Replacement therapies administered were also analysed. For surgical procedures (*n*=50), a receiver operator characteristic analysis showed that the minimal first dose of rFVIIa to avoid postsurgical bleeding during the first 24 hours was 22 μg/kg, and no less than two administrations. Prophylaxis was reported in 25 women with excellent or effective outcomes when performed with a total weekly rFVIIa dose of 90 μg/kg (divided as three doses).

Conclusion: Women with FVII deficiency have a bleeding disorder mainly characterized by mucocutaneous bleeds, which predicts an increased risk of ensuing gynaecological bleeding. Systematic replacement therapy or long-term prophylaxis with rFVIIa may reduce the impact of menorrhagia on the reproductive system, iron loss and may avoid unnecessary hysterectomies.

Introduction

Autosomal recessive bleeding disorders (ARBDs) occur as frequently in women as in men, but women may experience more bleeding than men because the gynaecological and obstetric challenges to haemostasis add an important additional burden to the background bleeding related to the haemostatic defect. In addition, when tested for haemostatic abnormalities, as many as 20% of women with excessive menstrual bleeding (menorrhagia) are found to have a bleeding disorder, be it frequent (von Willebrand disease [vWD]) or rare [1]. This is because menstruation and ovulation are associated with an increased risk of bleeding, as are pregnancy and delivery, or gynaecological and endocrine pathologies [1,2].

Menorrhagia is the most common bleeding symptom in women of reproductive age with ARBDs [3-8], represents a very frequent cause of iron deficiency [1,3,6,9-12] and carries a high negative impact on the quality of life [2,7]. Furthermore, other frequent gynaecological problems, such as uterine fibroids, are more likely to be symptomatic because of the increased bleeding tendency. In addition to menorrhagia, irregular menstrual cycles, breakthrough spotting, haemorrhagic ovarian cysts and endometriosis are other common gynaecological abnormalities reported in women with ARBDs [2,3,6]. With reference to the obstetric problems, bleeding may persist throughout pregnancy [12], especially when the haemostatic defect is severe.

Factor VII (FVII) deficiency is an ARBD with an estimated incidence of 1/300 000 to 1/500 000 in the general population [8,13-15]. The bleeding phenotype of affected patients is highly variable, ranging from asymptomatic patients to those who may experience life-threatening bleeding episodes [8,13]. Treatment of the most frequently occurring gynaecological conditions is mostly based on the limited experience of each

treating centre or on infrequent reports. For menorrhagia, the therapy options have recently changed from more conservative medical approaches, with antifibrinolytics and hormones, to replacement therapy (RT) and prophylaxis [2,15,16]. This shift towards a rational, replacement-based approach is likely to change clinical practice that, until recently, frequently adopted surgical approaches including endometrial ablation [17] or hysterectomy [18].

Currently, available data also indicate that while FVII plasma levels rise during pregnancy in normal women, no such increase is observed in homozygous patients and only a moderate rise is observed in heterozygous individuals [12]. As a consequence, women with FVII deficiency may develop bleeding not only during pregnancy but also postpartum [1,12,13,19].

Due to the rarity of this autosomally inherited bleeding disorder and the lack of evidence-based data, we collated and analysed data from two large, fully compatible registries—Seven Treatment Evaluation Registry (STER) and the International Registry on Congenital FVII Deficiency (IRF7); *n* = 449 patients; the aim of this analysis was to describe the reported clinical picture of FVII deficiency in women and highlight any sex-related differences. In addition, we reviewed the treatment options reported in the STER for the bleeds and the most common gynaecological and obstetric bleeding reported.

Materials and methods

Data reported for patients with FVII deficiency in IRF7 and STER were analysed using the same method as that adopted for a previous study [13]. The primary aim of IRF7 was to collect and describe data on inherited FVII deficiency clinical phenotype and genetic mutations, while STER was intended to describe replacement treatment

modalities and outcomes. Both databases gathered homogenous demographic and clinical history data on bleeding symptoms (site, frequency, entity, treatment) related to two different cohorts of patients with inherited FVII deficiency; thus, they can be merged for descriptive purposes. The registry protocols were approved by the Institutional Review Board of L'Aquila University Hospital. The STER protocol was published on *http://clinicaltrials.gov* (NCT01269138).

FVII coagulant activity (FVII:C) measurements were assessed at each participating centre. In 98% of the centres, high-sensitivity thromboplastins (International Sensitivity Index ≈ 1) were employed. Screening for inhibitors to FVII was performed at a central laboratory [20].

As FVII:C levels higher than 26% have an uncertain clinical relevance to bleeding events [21], individuals with FVII:C >26% were excluded from the analyses. Patients were classified in accordance to previously published criteria into residual FVII:C subgroups (<3%, 3–26%, >26%) and also by clinical phenotype as either major bleeders, minor bleeders or asymptomatic patients [13].

Surgical procedures were classified as either minor or major according to standard criteria [22]. For each procedure, the following data about RT schedule were evaluated: (i) RT duration (days), (ii) number of RT injections, (iii) first dose and (iv) total RT dose per day.

As the majority of RT was performed with rFVIIa (Novoseven®, Novo Nordisk, Bagvaerd, Denmark), efficacy evaluation was limited to this RT type and 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. In the case of prophylaxis: no bleeds in between the doses.
- *Effective:* More than one administration was needed to obtain the same results as above. In the case of prophylaxis: >50% reduction in the number of bleeds.
- *Partially effective:* More than one administration was needed, but symptoms subsided slowly and the return of limb and joint mobility was partial. In the case of prophylaxis: <50% reduction of the number of bleeds.
- *Ineffective:* No changes.
- *Not evaluable:* No elements for evaluation.

Statistical analysis

Data obtained from the two databases were analysed following a quality and consistency check of each value. Continuous data were expressed as mean ± standard deviation and categorical variables as percent. Continuous variables were compared using an independent sample *t*-test. For data with a skewed distribution, non-parametric tests were used. The chi-square test was employed to analyse categorical data. A Cox regression analysis was used to determine the risk (hazard ratio [HR]) of developing any gynaecological bleed according to FVII:C. A logistic regression model was also used to explore whether lifelong gynaecological bleeding may be predicted by the type of bleeding presented at the time of FVII deficiency diagnosis. For surgery, as all bleeding

episodes occurred during the first postoperative day, the receiver operating characteristic analysis was performed for the first dose, number of doses and the total dose given on the first day, with a sensitivity set at 100%. All results are expressed as two-tailed values with statistical significance reported as $P < 0.05$. Statistical analysis was performed with the SPSS 16 system (SPSS Inc., Chicago, IL, USA). Due to the exploratory nature of the study, correction for multiple tests was not conducted.

Results

Bleeding phenotype and gender comparisons

A complete merging of both databases included 755 patients, after the exclusion of cases not reporting the variables analysed, 449 patients (215 males, 234 females) were included in the current analysis. Table 1 reports the clinical and demographic characteristics of the study population. A significant difference in FVII:C levels was observed between men and women. Another significant difference was noted in the distributions of the clinical severity classes, both at presentation and with reference to the lifelong analysis.

As shown in Table 2, women who experienced gynaecological bleeding were diagnosed with FVII deficiency earlier and had significantly lower FVII:C than did women without gynaecological bleeding. The association between gynaecological bleeding and the other mucous membrane-related bleeds is also shown in Table 2. In addition, a multivariate analysis confirmed this association and showed that, after adjusting for age, age at diagnosis, age at first symptom and residual FVII levels, a history of gum bleeds, epistaxis and easy bruising (excluding the most severe bleeds, where a lifespan up to the age of menarche is rarely achieved) is a strong predictor of ensuing gynaecological bleeding with an HR of 12.8 for minor and 18.6 for major bleeders.

The impact of FVII:C level on the lifelong gynaecological bleeding-free survival was clear; women with <3% FVII:C showed a significant increased risk of lifelong gynaecological bleeding compared with those with 3–26% FVII:C (HR = 2.802, 95% confidence interval [CI] 1.308–6.002, *P* = 0.008).

Surgical procedures

Sixty-three surgical procedures (26 major, 37 minor) performed in 53 women (mean age 38.9 ± 22.0 years) were analysed and are summarized in Table 3, which also includes the main RT data reported. A total of five perioperative bleeding episodes occurred, all in patients with <1% FVII:C. The receiver operating characteristic curve analysis was performed on 50 patients who received rFVIIa for RT performed on the first day of surgery; this analysis showed that a first dose of 22 µg/kg (area under the curve [AUC] = 0.816, CI 0.68–0.91, *P* = 0.0031) and no less than two administrations (AUC = 0.7, CI 0.55–0.82, *P* = 0.024) was the minimal treatment schedule able to avoid excessive bleeding. The first day total dose (45 µg/kg), although not significant, supported the previous findings (AUC = 0.66, CI 0.51–0.69, *P* = 0.09). Anti fibrinolytic agents (tranexamic acid) were administered as concomitant medication during surgery in 16 case.

Replacement therapy for spontaneous bleeds and prophylaxis

Table 4 reports the RT used for episodically occurring bleeds for each type of haemorrhage. The analysis, again, was restricted to RTs performed with rFVIIa.

Anti fibrinolytic agents (tranexamic acid) were administered as concomitant medication to control spontaneous bleeding episodes in 6 cases.

Prophylaxis regimens were performed in 25 women with FVII deficiency. For those patients treated with rFVIIa (*n* = 15, excluding menorrhagia as an indication for prophylaxis), the outcome was excellent (no bleeds reported) or effective (>50% reduction of the number of bleeds), with a median dose of 90 μg/kg rFVIIa divided into three doses per week [16].

Discussion

This paper reports on the first comprehensive study focusing on the clinical and therapeutic scenarios of women with a FVII deficiency. In terms of the general demographic data, the only significant difference between male and female patients with FVII deficiency was FVII:C levels, which were lower in women (Table 1)—a finding we have previously reported [8,16], but for which we cannot offer an explanation, especially if one takes into account that there is a significantly higher prevalence of major bleeders in males (Table 1). This difference between male and female patients in severity of bleeding phenotypes was consistent both at disease presentation and for the lifelong bleeding analyses. Of note, after exclusion of the leading gynaecological symptom in female patients, menorrhagia, a clear difference in the clinical phenotype between men and women with FVII deficiency was evident and characterized by a higher prevalence of mucocutaneous bleeds in women with FVII deficiency than men.

When considering the lifelong history of women with a FVII deficiency, menorrhagia was the most prevalent bleed, present in approximately 50% of patients, slightly lower than that reported in vWD [4,5,23]; the same holds for menorrhagia as a presentation

symptom in comparison with vWD [2]. However, these differences should be taken with caution, given the study type and the subjectivity underlying surveys focused on this particular symptom [11,24,25]. Here, all 28 reported to have gynaecological bleeding as the first bleeding manifestation (71% related to the menarche) experienced recurrences of gynaecological bleeding; for the other 81 women with FVII deficiency who had other disease presentations, gynaecological bleeds occurred at different ages (range 11–79 years), mostly during the fertile years (75%).

The occurrence of mucocutaneous bleeds at disease presentation was strongly predictive for gynaecological bleeding. This means that a girl who is symptomatic is at very high risk (HR = 12.8 for minor and 18.6 for major bleeders) of developing menorrhagia at the menarche or afterwards. Therefore, her family should be duly alerted in preparation for the menarche. Our analyses found that FVII:C was an important element useful for the prediction of gynaecological bleeding. However, the difference between women with and without gynaecological symptoms is likely to be explained by determinants other than FVII:C levels, possibly endocrine. This possibility makes the role of the missing clotting factor levels in determining excessive uterine blood loss in clotting disorders unclear; in fact, there is also a high prevalence of menorrhagia in women who are haemophilia carriers who, by definition, have intermediate to subnormal FVIII/IX levels [4].

In our cohort, 26 of the surgical procedures reported in the STER were ‘major’ and 37 were ‘minor’. For major surgical interventions, a slightly higher first day rFVIIa dose was used in comparison with the minor interventions/invasive procedures (39 vs. 32 μg/kg), but the number of RT administrations (18 vs. 2) was clearly higher, findings similar to our previous reports [26,27]. As bleeding complications only occurred during

the first 24 postoperative hours and baseline FVII:C levels did not help to predict bleeding (all <1%), the analysis restricted to the early RT period showed that non-bleeders were given a higher first dose (at least 22 μg/kg) and no less than two doses in comparison to those patients who had bled. These findings highlight the importance of using a sufficiently effective RT schedule during the first 24 postoperative hours to prevent postoperative bleeding [26,27].

Regarding the obstetric and gynaecological interventions reported in our study (n = 9), it is of interest that four of these were hysterectomies with or without ovariectomy. The issue of hysterectomy in bleeding disorders is not a negligible one [2,28,29], with most of the available data coming from women with vWD; in a case-control study [29], 26% of women had undergone a hysterectomy procedure compared with 9% of the controls. Of note, pathological specimens from women with longstanding menorrhagia often reveal uterine fibroids, endometrial hyperplasia and polyps, together with a high prevalence of endometriosis [2]. The most plausible cause of the latter complication was postulated to be due to retrograde menstrual flow [30,31].

In our cohort, postpartum bleeding was reported in four women (median age 21.13 years; range: 19–33; FVII:C range: 3.4–12.0%). However, as we do not have a denominator (number of deliveries), we were unable to calculate the incidence of this bleeding event. Recently, a systematic review on 94 deliveries in women with FVII deficiency [32] reported a 13% incidence of postpartum bleeding in women who did not receive prophylaxis with rFVIIa (higher in caesarean sections than in vaginal deliveries) vs. 10% of those who were given RT; the lack of a significant difference led the authors to conclude that in this clinical setting, prophylaxis should not be considered as

mandatory, but an individualized approach should be used based on the response to previous haemostatic challenges and the mode of delivery.

Spontaneous bleeding episodes (Table 4) were grouped by type; most of the bleeds (menorrhagia, haemarthrosis, epistaxis and hematomas) were treated for 1 day with a total rFVIIa dose ranging from 30–45 μg/kg with either excellent (one dose) or effective (more than one dose) outcomes. Hence, these findings confirm our previous suggestion [15] that RT schedules based on 1 day and intermediate rFVIIa doses can be safely proposed for these common bleeds. Due to the small number of life-threatening bleeds in our cohort (in particular, CNS bleeds), these data do not allow any recommendation on the protocols to use for these events. However, such severe bleeds require individualized long-term, high-dose treatments, and we believe that prophylaxis should be recommended as soon as possible [16].

The efficacy of antifibrinolytic agents in menorrhagia, either alone or compared with other medical interventions, has been recently reviewed [33] and showed a greater efficacy of these agents as compared with other interventions (including the oral luteal phase progestagens), but not intrauterine administration of levonorgestrel. Oral progestagens, combined hormonal contraceptives and the levonorgestrel intrauterine system are currently proposed as a first conservative therapeutic choice in women with bleeding disorders [2], although no comparative trials against antifibrinolytics in congenital bleeding have been conducted. In our study, RT was employed mostly without antifibrinolytics and no difference in outcome was observed with the combined use.

Of note, ‘prophylaxis’ carried out in women with FVII deficiency suffering from menorrhagia with replacement treatment given either on day 1 or the first 2 days of the

menses for long periods of time (up to 178 months in one patient) yielded excellent results, in keeping with our previous findings in which prophylaxis reduced blood losses by up to 80% [11]. One then questions why this should not be the current strategy for women with ARBD and menorrhagia when this very common bleed occurs from the menarche, and no endocrine abnormalities are found. This treatment strategy has a low cost, improves the quality of life and may reduce secondary gynaecological complications without interfering with fertility. The ultimate goal could be that of reducing or abolishing the practice of hysterectomy as a mean for controlling gynaecological bleeding.

Finally, a total of five adverse events were recorded in four patients: one inhibitor [20], three re-bleeding episodes (unrelated to therapy as these occurred 4 weeks after treatment) and one event of facial nerve paresis (possibly unrelated to therapy). Considering the number of patients, the array of clinical bleeds and the large number of administrations, RT, at least in this setting, may be considered very safe.

Conclusion

We have provided evidence that women with FVII deficiency have a bleeding disorder mainly characterized by mucocutaneous haemorrhage. Hence, the differential diagnosis against other ARBDs cannot be done on the basis of the bleeding history. Mucocutaneous bleeding was associated with a high risk of gynaecological bleeding during and after the menarche. FVII:C levels of <3% was a further predictor of gynaecological bleeding. Systematic replacement therapy or long-term prophylaxis appears to reduce the impact of menorrhagia on the reproductive system, reduce iron loss and may avoid unnecessary hysterectomies.

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MN had the idea for the manuscript, enrolled patients and wrote the manuscript. MNDDM performed the statistical analyses and drafted the manuscript. AD participated in the statistical analysis, study design, data collection and review of the manuscript. AB, MG-B, JI, J-FS, GA, GK, MK, TS, ARdS, RD, AC and MAB participated in the data collection and reviewed the manuscript. GM ideated and conducted the IRF7 and STER studies and critically revised the paper.

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Table 1. Clinical and demographic characteristics of the study population.

General	Males (n = 215)	Females (n = 234)	*P*
Age, years	29.0 ± 21.3 (median: 24, range: 1–86)	31.1 ± 20.5 (median: 27.5, range: 1–86)	0.197*
Age at diagnosis, years	16.4 ± 18.5 (median: 8.01, range: 1–79.9)	18.8 ± 17.2 (median: 13.7, range: 1–77.8)	0.084*
Age at first symptom, years	12.2 ± 17.4 (median: 4.69, range: 1–80)	12.0 ± 15.1 (median: 6.3, range: 1–77.8)	0.133*
FVII:C levels, %	7.72 ± 7.76 (median: 3.4, range: 0.01–25.0)	4.99 ± 6.40 (median: 2.0, range: 0.01–25.0)	<0.001*
Presentation, *n* (%)			
Asymptomatic	73 (34.0)	49 (20.9)	<0.001
Minor bleeders	96 (44.7)	157 (67.1)	
Major bleeders	46 (21.4)	28 (12.0)	
GI	10 (4.7)	9 (3.8)	0.815
CNS	28 (13.0)	11 (4.7)	**0.002**
Haemarthrosis	8 (3.7)	8 (3.4)	1.000
Umbilical	6 (2.8)	9 (3.8)	0.606
Rectal	7 (3.3)	1 (0.4)	**0.031**
Hematoma	3 (1.4)	8 (3.4)	0.225
Menorrhagia	–	28 (12.0)	–
Haematuria	2 (0.9)	0	0.229
Gum bleed	4 (1.9)	13 (5.6)	**0.048**
Epistaxis	44 (20.5)	56 (23.9)	0.427

Easy bruising	9 (4.2)	13 (5.6)	0.522
Other	1 (0.5)	4 (1.7)	0.374
Postsurgical	20 (9.3)	25 (10.7)	0.641
Lifelong, *n* (%)			
Asymptomatic	72 (33.5)	43 (18.4)	<0.001
Minor bleeders	68 (31.6)	121 (51.7)	
Major bleeders	75 (34.9)	70 (29.9)	
GI bleeding	26 (12.1)	27 (11.5)	0.884
CNS bleeding	34 (15.8)	19 (8.1)	**0.013**
Haemarthrosis	46 (21.4)	39 (16.7)	0.228
Hematoma	34 (15.8)	51 (21.8)	0.118
Menorrhagia	–	109 (46.6)	–
Haematuria	13 (6.0)	14 (6.0)	1.000
Gum bleed	43 (20.0)	85 (36.3)	**<0.001**
Epistaxis	82 (38.1)	105 (44.9)	0.152
Easy bruising	53 (24.7)	95 (40.6)	**<0.001**
Postsurgical	21 (9.7)	29 (12.4)	0.468

FVII:C, factor VII coagulant activity; GI, gastrointestinal; CNS, central nervous system.

**P* for non-parametric comparisons (Mann–Whitney test).

Table 2. Univariate analysis of lifelong bleeding episodes in women with and without gynaecological bleeding.

General	Gynaecological bleeding (*n* = 109)	No gynaecological bleeding (*n* = 125)	*P*
Age, years	23.9 ± 20.5 (median: 16.0, range: 1–79)	39.2 ± 17.3 (median: 40, range: 11–86)	<0.001*
Age at diagnosis, years	14.2 ± 15.5 (median: 7.43, range: 1–68.8)	22.8 ± 17.6 (median: 20.0, range: 1–77.8)	0.002*
Age at first symptom, years	11.2 ± 15.2 (median: 5.24, range: 1–68.8)	12.9 ± 14.8 (median: 7.64, range: 1–77.8)	0.043*
Residual FVII, %	3.7 ± 5.27 (median: 1.4, range: 0.01–25)	6.11 ± 7.08 (median: 2.7, range: 0.01–25.0)	0.004*
Lifelong, *n* (%)			
Major bleeders	27 (24.8)	43 (34.4)	**<0.001**
Minor bleeders	82 (75.2)	39 (31.2)	
GI bleeding	8 (7.3)	19 (15.2)	0.067
CNS bleeding	7 (6.4)	12 (9.6)	0.474
Haemarthrosis	18 (16.5)	21 (16.8)	1.000
Haematoma	24 (22.0)	27 (21.6)	1.000
Haematuria	8 (7.3)	6 (4.8)	0.425
Gum bleed	54 (49.5)	31 (24.8)	**<0.001**
Epistaxis	65 (59.6)	40 (32.0)	**<0.001**
Easy bruising	60 (55.0)	35 (28.0)	**<0.001**
Postsurgical	17 (15.6)	12 (9.6)	0.245

FVII, factor VII; GI, gastrointestinal; CNS, central nervous system.

*P for non-parametric comparisons (Mann–Whitney test).

Table 3. Characteristics of surgical procedures performed in female subjects.

Type of surgery	**Total (*n* = 63)**	**Major surgical procedures (*n* = 26)**	**Minor surgical procedures (*n* = 37)**
		Surgery data	
Obstetric and gynaecologic*	9	9 (6 rFVIIa, 3 pd-FVII)*	–
Orthopaedic	4	4 (3 rFVIIa, 1 pd-FVII)	–
Ear, nose and throat	3	3 (2 rFVIIa, 1 pd-FVII)	–
General surgery	6	6 (5 rFVIIa, 1 pd-FVII)	–
Urologic	2	2 (2 rFVIIa)	–
Cardiac	1	1 (1 rFVIIa)	–
Neurosurgery	1	1 (1 rFVIIa)	–
Oral surgery	17	–	17 (15 rFVIIa, 2 pd-FVII)
Eye surgery	2	–	2 (2 rFVIIa)
Endoscopic procedures/biopsies	18	–	18 (13 rFVIIa, 5 pd-FVII)
Treatment data (only rFVIIa; median and range)	**(*n* = 50)**	**(*n* = 19)**	**(*n* = 31)**
Number of days	1 (1–9)	1 (1–9)	1 (1–3)
Number of doses	3 (1–92)	18 (1–34)	2 (1–31)
Total first day dose	39 (10–3026)	39 (10–3026)	32 (11–400)
Concomitant antifibrinolytics	28 (56%)	13 (68.4%)	15 (48.3%)
Prophylaxis with low	4 (7.8%)	2 (10.5%)	2 (6.4%)
Perioperative thrombosis	0	–	–
Perioperative bleeding	5 (10%)	–	5 (16.1%)†
Need for red blood cells	6 (11.8%)	5 (26.3%)	1 (3.2%)

In-hospital stay (days)	5.0 (1–22)	8.5 (2–22)	2 (1–12)

rFVIIa, recombinant factor VIIa; pd-FVII, plasma-derived factor VII.

*See Table 4 for details.

†Three with antifibrinolytics, two without.

Table 4. Replacement therapy for spontaneous bleeding episodes (doses reported and outcome refer only to rFVIIa treatment).

		Patient profile			Treatment profile					
Bleeding type (number of patients)	**Bleeds, *n***	**Age, years** *Median (range)*	**FVII:C, %** *Median (range)*	**Bleeding profile** *Major/ minor*	**Drug**	**Duration of RT, days** *Median (range)*	**Number of doses** *Median (range)*	**Total dose, µg/kg** *Median (range)*	**Mean daily dose, µg/kg** *Median (range)*	**Outcome**
Menorrhagia (10)	15	22 (11–46)	<1 (<1–4)	6/9	14 rFVIIa 1 pd-FVII	1 (1–6)	2 (1–8)	45.5 (20–240)	27.5 (13–120)	10 excellent, 4 effective
Haemarthrosis (8)	9	11 (5–72)	1.3 (<1–3)	9/0	8 rFVIIa 1 FFP	1 (1–1)	1 (1–7)	42.5 (18–240)	42.5 (18–80)	6 excellent, 1 effective, 1 partly effective
Epistaxis and gum bleeding	8	13 (5–54)	1 (<1–2.7)	5/3	5 rFVIIa 2 pd-FVII	1 (1–1)	1 (1–2)	30 (26.6–	30 (26.6–66)	4 excellent, 1 effective

(5)				1 FFP			66)		
Haematomas (7) *(muscle and subcutaneous)*	7	4 (0.5–59)	2.1 (<1–23.6)	3/4	5 rFVIIa 2 FFP	1 (1–1)	2 (1–3)	30 (26–75)	30 (26–75)	4 excellent, 1 effective
CNS (3)	4	<1 (<1–45)	1 (<1–1)	4/0	3 rFVIIa 1 FFP	12 (1–15)	68 (8–84)	2.650 (125–3710)	176.7 (125–309.2)	3 effective
Easy bruising (2)	4	13 (7–13)	2 (1–2.5)	0/4	4 FFP	–	–	–	–	Not evaluable
Other (4) *(GI, haematuria haemo-peritoneum)*	4	6 (0.1–25)	<1 (<1–5)	3/1	3 rFVIIa 1 pd-FVII	2 (1–11)	8 (3–52)	240 (90–1716)	120 (90–156)	3 excellent

FVII:C, factor VII coagulant activity; RT, replacement therapy; FFP, fresh frozen plasma; pd-FVII, plasma-derived factor VII; rFVIIa, recombinant factor VIIa.