LETTER TO THE EDITOR

Replacement therapy in inherited factor VII deficiency: occurrence of adverse events and relation with surgery

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The treatment paradigm for bleeding management in patients with congenital bleeding disorders is Replacement Therapy (RT), based on the substitution of the missing coagulation factor, with the aim of correcting the clotting defect. For the management of patients with factor VII (FVII) deficiency, a rare bleeding disorder, a number of therapies are available, including plasma or plasma-derived products as well as recombinant products [1,2]. However, information regarding optimal treatment schedules, treatment limitations and Adverse Events (AEs) is currently limited to anecdotal reports [3–8]. As a consequence, RT administration is influenced by factors such as the rarity of the disorder, the type, availability and supply of products, as well as economic and geographical factors.

It is taken for granted that all RT types and schedules are associated with potential side-effects, and there is no doubt that the management of patients with bleeding disorders can be improved by reducing the occurrence of AEs and their severity. Awareness of AEs is indeed a relevant issue in the management of rare bleeding disorders, where data collection, especially in a prospective fashion, is very difficult.

The Seven Treatment Evaluation Registry (STER) has prospectively collected a large amount of information on the management of patients with congenital FVII deficiency [9–13]. The aim of this study was the systematic analysis of AEs related to treatments, for prophylaxis [9], surgical interventions [10,12] and spontaneous or traumatic bleeding episodes [11].

Patients with congenital FVII deficiency managed for a large array of clinical indications were investigated for RT-related AEs during the 8-year duration of the STER (deadlock date: February 28th, 2012). STER was a prospective, observational, multicentre, web-based registry created to collect and describe data on treatment modalities and outcomes in patients with this rare bleeding disorder. All treatment procedures were in accordance with the ethical standards and approved by the Ethics Committee of L'Aquila University Hospital (coordinator's institution) and the committees of all the other enrolling centres. Decisions on type of RT and schedules were autonomously taken by enrolling physicians.

Because of different viral ecologies, treatment attitudes and laboratory issues, pharmacovigilance was limited to non-blood-borne virus-related AEs; decisions on RT type and schedules were taken autonomously by the enrolling physicians. The STER study protocol was designed to capture the following elements related to AEs: clinical description, evaluation of severity (serious or non-serious), potential association with type of treatment (likely or unlikely) and outcome (including mortality for any reason). Thrombosis diagnosis (venous or arterial) was based on clinical suspicion and confirmed by imaging. FVII: c was determined at baseline and 15 min after the first RT administration for the treatment reported. STER protocol was designed to centrally determine inhibitors at the following time points: first enrolment (before RT administration), 30 days follow-up after the reported RT and when needed for clinical suspicion. Screening for inhibitory antibodies to FVII was conducted in a

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centralized fashion [4,13]; only baseline samples with FVII:c <4% were considered for inhibitor assay. Enrolling physicians were asked to carefully describe the type of AE, timing of occurrence after RT, clinical management and outcome. AEs were evaluated at the time of treatment and at the 30-day follow-up visit (or later if needed). Data were obtained from the STER database and analysed following a data quality and consistency check according to the STER data-management plan. We calculated the cumulative incidence rate of AEs in our cohort as the number of new cases per population at risk in a 8 years observational period and the incidence density rate (or person-time incidence rate) as number of new cases per population at risk in a given time period when the denominator is the sum of the person-time of the at risk population. With regard to every type of AE, we also calculated the prevalence in our cohort for specific adverse events as the proportion of cases in the population at the end of the study. Analyses were performed using the MEDI-CAL® software version 7.4.1.2 (http: www.med-calc.org). We here focus on inhibitor development and thrombosis, being these considered the most relevant AEs related to RT. Other side-effects reported after RT ($n = 11$) consisted mainly in re-bleeding ($n = 4$) and aspecific symptoms like headache, virosis and fever, judged as unlikely related to RT ($n = 7$). STER overall enrolled 225 patients with congenital FVII deficiency and a total of 312 treatments were administered: recombinant activated FVII (rFVIIa, Novo Seven®, Novo Nordisk A/S, Denmark, $n = 245$ [78.5% of all replacement therapies]); plasma-derived FVII concentrates (pd-FVII, Facteur VII™ LFB, Courtaboef, France or Provertin-UM TIM3™, Baxter, Vienna, Austria; FVII NF, Baxter, $n = 31$, 9.9%); Fresh Frozen Plasma (FFP), $n = 30$, 9.6%); Prothrombin Complex Concentrate (PCC, Prothromplex TIM 3, Baxter; Prothromplex Total TIM 4, Baxter, $n = 5$, 1.6%), and in one case FEIBA (Baxter). The AE's cumulative incidence was (2.2%, CI 0.6–3.9%) and the incidence density rate was 1.6% (CI 0.0–2.5%) per year. As for FVII inhibitors, 115 patients were centrally tested using a standardized modification in the Bethesda assay. Inhibitors occurred in two of those patients in whom a centralized screening could be done ($n = 125$); two other inhibitor patients were enrolled in the STER but inhibitor could not be centrally confirmed for logistical reasons. Three of the four reported inhibitors were detected during prophylaxis with rFVIIa, in two young boys at the age of 5 years and 1 year, respectively, and in one infant (a 5 months old male).

All cases had a very severe bleeding phenotype (epistaxis, easy bruising, gastrointestinal bleeding, CNS bleeding, subcutaneous and muscle haematoma). Baseline FVII:c levels were 2, 1.3 and <1% respectively. All the three patients were previously exposed to multiple FFP infusions and prophylaxis with rFVIIa was instituted to prevent CNS (in two cases) and GI (in one case) bleedings. The immune response in FVII deficiency was not complicated by anaphylactic reactions. Prophylaxis was continued in all three patients without any safety problem or reported dose-adjustment. All the patients were high responders with peak titres of between 34 and 68.3 BU mL^{-1} (Table 1) at the last available follow-up (1 month after detection).

One case of inhibitor was detected in adulthood, in a 53 year-old woman previously treated with FFP, pd-FVII and PCC for recurrent bleeding episodes (mainly gynaecological). Inhibitor was discovered when the patient underwent multiple dental extractions, the patient was treated with rFVIIa given at an initial dose of 30 µg kg^{-1} followed by eight consecutive boluses of 10 µg Kg^{-1}. Patients were not reported to undergo any specific treatment for inhibitor eradication (Table 1).

Thrombosis occurred in three patients: two cerebral infarctions and one superficial vein thrombosis (1% of treatments). Dosing and treatment schedules are shown in the Table 1.

In the first case (M/8), treated for the evacuation of left cerebellar haematoma, RT with rFVIIa lasted 8 days; rFVIIa was administered immediately before the procedure and for the following 7 days at a dose of 18 µg Kg^{-1} every 6 h. FFP was than administered up to 16 days post procedure at a dose of 10 U Kg^{-1}, every 6 h.

In the second case (M/23), treated for knee replacement, RT with rFVIIa was given before the procedure and every 12 h in the following 24 h after orthopaedic surgery at a dose of 30 µg Kg^{-1}. Superficial Vein Thrombosis (SVT), confirmed with Doppler ultrasounds, involved the cephalic vein of the right arm.

In the third case (M/53), treated for kidney transplant, rFVIIa was administered 30 min before the procedure and 15 min thereafter. After 1 h, the dose of rFVIIa was empirically lowered to 22.5 µg kg^{-1}; after 4 h, rFVIIa was given at 15 µg kg^{-1}. The following RT administrations occurred at 8, 18, 24 and 30 h after the first one, namely at a doses of 15 µg kg^{-1}. Starting from 36 h, rFVIIa (15 µg kg^{-1}) was administered every 6 h until 96 h (day 4), when the same dose was injected twice a day for the following 6 days. The patient was discharged under immunosuppressive drugs. At 30 days follow-up visit he presented with a paralysis of the right leg started 48 h before admission, a CT scan confirmed the involvement of the left anterior cerebral artery and the patient was treated with Low Molecular Weight Heparin (LMWH) at prophylactic dose for 2 weeks, without any bleeding complication and a partial relief of paralysis. Further RT was not administered during LMWH.

Table 1. Thrombosis and inhibitors reported to the STER.

Sex/Age	Replacement therapy	FVII:c(%) 0′	FVII:c (%) 15′	Clinical setting	Event	Timing	Severity/Relation to replacement
Thrombosis							
M/8	rFVIIa 15 μg Kg^{-1} × 43, FFP 10 IU × 13	2.3	320	Neurosurgery	Cerebral infarct	8th day	Serious/Likely
M/23	rFVIIa 30 μg Kg^{-1} × 3	6	99	Orthopaedic surgery	SVT	1st day	Non-serious/ Likely
M/53	rFVIIa 30 μg kg^{-1} × 2, 22.5 μg kg^{-1} × 1, 15 μg kg^{-1} × 28	4.8	380	Renal transplant	Stroke	30 days	Serious/Likely
Inhibitors							
F/53* (p.A354V; p.464Hfs)	rFVIIa[†,‡] 30 μg Kg^{-1} × 1, 10 μg Kg^{-1} × 8	<1[§]	/	Minor surgery	High titre10–20 BU	Postoperatively	Serious/Likely[§]
M/5* (p.Ser112 Stop)	rFVIIa[†,‡] 30 μg Kg^{-1} × 21 days	2[§]	/	Prophylaxis for CNS bleeding	High titre 38-68.3 BU	3 months[¶]	Serious/Likely
M/0.5	rFVIIa[†,‡] 65 μg Kg^{-1} × 1/week	1.3[§]	/	Prophylaxis for CNS bleeding	High titre 5.5-60 BU	5 months[¶]	Serious/Likely
M/1	rFVIIa[†,‡] 31 μg Kg^{-1} × 3/week	<1[§]	/	Prophylaxis for GI bleeding	High titre 32–72 BU	1 month[¶]	Serious/Likely

Brackets report FVII gene mutation, SVT, superficial vein thrombosis. Age is expressed in years.
*inh. detected centrally.
[†]Schedule refers to RT prior to inhibitor(inh). detection.
[‡]All patients received different treatments (pdFVII, FFP) before inh. detection.
[§]Baseline levels.
[¶]Age at inhibitor screening.
BU=Bethesda Units.

Inhibitors to FVII were considered the most important side-effect associated with RT; we, therefore, performed a screening using a standardized modification in the Bethesda assay in a centralized fashion [4,6,13]. Of the two inhibitors screened and confirmed by the Central Laboratory, one had been previously detected; one was a *de novo* event. FVII gene mutation is available only for two patients with inhibitors (one with a missense mutation plus one codon deletion and another homozygous for a nonsense mutation).

Inhibitor occurrence in FVII deficiency can be considered at least as rare as that currently reported in haemophilia B [6], where a prevalence of 2–3% is accepted. Comparison to FIX deficiency is the most reasonable one, due to a high comparability in the gene and protein structures of FIX and FVII, even though severe gene defects, such as large deletions, have not been reported in patients with FVII deficiency [14]. Another substantial difference between the two bleeding disorders is the occurrence of anaphylactic reactions, a severe clinical issue in patients with haemophilia B, that is absent in patients with inhibitors to FVII, as confirmed by the fact that prophylaxis in FVII-deficient patients, can be continued even in the presence of an inhibitor [13]. Two other cases of inhibitor were reported in the STER but inhibitor detection could not be determined in a centralized fashion. Considering the total number of patients enrolled in the STER (*n* = 225), the prevalence (1.8%) appears unchanged.

The prevalence rate of thrombosis in the STER was 1% (3/312 treatments). This prevalence is the same as that found in a retrospective study by our group [5].

Postinfusion FVII coagulant activity levels did not differ between those patients experiencing AEs and the other uncomplicated treatments (data not shown), and no relationship could be established between thrombosis occurrence and the dose of rFVIIa or patient' age. The association between gene mutations and the risk of thrombosis has been explored [5] but even if two common mutations (Arg364Gln and Ala354Val) have been frequently detected in patients with thrombosis, no specific association has been found [5]. Thrombophilias, such as FV Leiden, prothrombin gene mutation, antiphospholipid antibodies syndrome and elevated clotting FVIII levels, were present in some cases of FVII deficiency with thrombosis, but they did not seem to play a relevant role as risk factors for thrombosis, since thrombophilia markers appeared to have a similar prevalence in patients with and without thrombotic complications [5]. This study suggests that FVII deficiency does not provide protection from thromboembolism, either arterial or venous, especially in a surgical setting. The indication for thromboprophylaxis in high-risk patients (e.g. patients undergoing major surgery and high-dose RT) still needs to be formally evaluated, but anecdotal reports suggest that it does not increase the risk of bleeding [5].

An important issue regards the frequency of surgery as a clinical setting associated with AEs, at least in this report (57.1%). Considering the reported AEs and the other side-effects ($n = 11$, data not shown), surgical interventions appear to play a not negligible role in the occurrence of adverse events (RR 2.5, $P = 0.0574$, CI 0.97–6.54).

This study focusing on AEs checked prospectively in a large number of patients with FVII deficiency and over a large array of clinical settings highlights a low-to-very-low incidence of AEs. This indicates a very good safety-to-efficacy ratio, especially for rFVIIa, the most used replacement treatment.

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Author contributions

M. Napolitano and G. Mariani prepared the drafts and interpreted the data. A. Dolce maintained the database, performed the data analysis and generated the figure. A. Batorova, M. Giansily-Blaizot, N. Mirbehbahani., M.N.D. Di Minno, M.F. Lopez Fernandez, M. Karimi, P. Charoenkwan and K. Kavakli collected data, contributed to writing the results section of this manuscript, enrolled patients and collected samples. J. Ingerslev performed centralized determination of inhibitors and critically revised the methods section. GM, the STER Study Group coordinator, critically revised data and revised all the text versions. All authors have revised and approved the manuscript.

Disclosures

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